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EDITORIAL

Online pharmacies: buyer beware

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Key words

counterfeit medicines,
drug regulation, online
pharmacies

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Online pharmacies have been operating in Australia since the mid 1990s. Community pharmacy is now a mix of traditional pharmacies with little or no online presence, pharmacies that dispense through multiple channels but where physical presence remains the dominant characteristic (substantial number), and pharmacies that are only online. The internet gives access to overseas-based online pharmacies thus allowing a comparison of Australian sites to those overseas.

An Australian pharmacy business must address a number of regulatory and licensing requirements of the jurisdiction and of operational best practice. A prescription is needed for Schedule 4 and Schedule 8 medicines and the importation of controlled substances or products is prohibited.¹ The risks to consumers from online pharmacies not complying with these regulations include:

- fake or adulterated products with little therapeutic activity or unknown safety and efficacy
- inappropriate supply of narcotics and other controlled substances
- lack of supervision by a doctor or pharmacist
- lack of appropriate drug information
- failure in supply-chain protocols which may affect the quality of a medicine, e.g. lack of appropriately stored or expired medicines
- unlicensed premises and staff.

Fake or rogue online pharmacies represent a danger to consumer health. In 2014, the US Government Accountability Office estimated that there were

36 000 rogue internet pharmacies. These pharmacies generally supply drugs without a prescription and may or may not employ pharmacists. They are rarely licensed in the jurisdiction where they are located. To all intents and purposes they are not pharmacies and may not even have a shopfront.²

A recent UK study of 113 online pharmacies selling diazepam, fluoxetine and simvastatin found that fewer than 25% were regulated and 80 were willing to sell prescription medicines without a prescription.³ The unregulated sites were more likely to provide safety information (cautions, adverse effects, drug interactions) suggesting that inclusion of some clinical knowledge should not serve as a guarantee of the seller's provenance. However, the unregulated sites were significantly less likely to provide the contact details of the pharmacy.³

Price tends to dominate the business model of online pharmacies with a focus on the mechanistic, technological and logistical aspects of supply. Most public discussion around online supply in the USA and Europe centres on price, market segmentation and domination, and economies of scale, rather than on the quality use of medicines.⁴

Anecdotally, both the USA and Australian experiences suggest that online pharmacies are able to offer cheaper medicines. In Australia, this does not include medicines that meet or exceed the consumer copayment as they are subsidised. Some consumers prefer the convenience of mail order, particularly in the rural and remote setting.

All studies and warnings from regulatory agencies emphasise the caution 'buyer beware'. As the UK Medicines and Healthcare Products Agency advises, 'Buying medicines online is a risk, many websites operate outside the legal requirements and you have no idea what you are getting and how it will affect you. You are gambling with your health.'⁵

Overseas online pharmacies appear to not offer the same level of personal contact that is required of Australian pharmacies, whether by standards or guidelines.⁶ An inspection of six online pharmacies verified by the US National Association of Boards of Pharmacy found no evidence for how consumers could contact the pharmacy for advice about medicines. The Australian situation is markedly different. The Pharmacy Board of Australia emphasises the quality use of medicines and states that:

The Board views the indirect supply of medicines, such as internet and mail-order

From the Editor



The treatment of hepatitis C is undergoing rapid change, thanks to the new regimens reviewed by Alex Thompson and Jacinta Holmes. While people may be tempted to order the new drugs from overseas, Bill Kelly urges caution with online ordering.

As hepatitis C can be sexually transmitted, it is also discussed by Catriona Ooi and David Lewis in their article on managing sexually transmitted infections.

Hepatitis C is also associated with injecting drugs such as opioids. There are controls on prescribing these drugs and Walid Jammal and Grace Gown warn about the medicolegal pitfalls for not following the regulations on opioid prescribing.

The supply of medicinal cannabis will also be tightly controlled. Bridin Murnion comments on the potential clinical applications of cannabis.

As cannabis causes cognitive impairment it is unlikely to be useful in patients with dementia. David Kitching tells us what can be used to treat depression in dementia.

dispensing, as less than the optimal way of delivering a pharmacy service because communication may be compromised. The Board recognises, however, that there are circumstances where these forms of communication are necessary in, or appropriate to, the patient's circumstances (e.g. in remote areas).

A pharmacist supplying medicines indirectly to a patient must comply with all relevant State or Territory, and Commonwealth legislation, the Pharmacy Board of Australia's *Guidelines for Dispensing of Medicines*, and established practice and quality assurance standards.⁷

The Australian Therapeutic Goods Administration (TGA) also publishes a warning regarding the potential dangers of online pharmacies (usually overseas) but does not conduct any regulatory review of internet sites.⁸ The TGA's position assists consumers in having greater confidence in Australian online pharmacy sites rather than those overseas.

Online ordering of medicines by consumers will remain a feature of the Australian pharmacy landscape, and high operational and professional requirements should ensure that medicines ordered from Australian registered online pharmacies meet Australian standards. Conversely, non-Australian sites offer little in the way of reassurance.

Australian health consumers should be vigilant of online pharmacies and standards and guidelines of the Pharmacy Board of Australia, the Pharmaceutical Society of Australia, and the accreditation requirements of the Quality Care Pharmacy Program need to be maintained. There should be appropriate governance of access to medicines, whether that be through a traditional walk-in pharmacy or via an online transaction. ◀

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REFERENCES

1. Therapeutic Goods Administration. Personal importation scheme. Canberra: Department of Health; 2015. www.tga.gov.au/personal-importation-scheme [cited 2015 Aug 12]
2. Internet pharmacies: Most rogue sites operate from abroad, and many sell counterfeit drugs. Washington (DC): US Government Accountability Office; 2014. www.gao.gov/products/GAO-14-386T [cited 2015 Aug 12]
3. Alwon BM, Solomon G, Hussain F, Wright DJ. A detailed analysis of online pharmacy characteristics to inform safe usage by patients. *Int J Clin Pharm* 2015;37:148-58.
4. Dudley J. The Internet Pharmacy. Presentation from the 46th AESGP Annual Meeting, Dubrovnik 2010. Slideshare.net; 2012. www.slideshare.net/JameswDudley/mail-order-and-internet-pharmacy-aesgp-presentation-james-dudley [cited 2015 Aug 12]
5. Websites closed in battle against illegal trade in medicines [press release]. London: Medicines and Healthcare Products Regulatory Agency; 2015. www.gov.uk/government/news/websites-closed-in-battle-against-illegal-trade-in-medicines [cited 2015 Aug 12]
6. The Pharmaceutical Society of Australia. Professional Practice Standards – Version 4 – June 2010. Canberra: Pharmaceutical Society of Australia; 2010. www.psa.org.au/download/standards/professional-practice-standards-v4.pdf [cited 2015 Aug 12]
7. Pharmacy Board of Australia. Guidelines for dispensing of medicines. Melbourne: Pharmacy Board of Australia; 2010. www.pharmacyboard.gov.au/Codes-Guidelines.aspx [cited 2015 Aug 12]
8. Therapeutic Goods Administration. Buying medicines and medical devices over the internet. Canberra: Department of Health; 2015. www.tga.gov.au/community-qa/buying-medicines-and-medical-devices-over-internet [cited 2015 Aug 12]

Online pharmacies: a consumer perspective

While the power of the internet has proved a terrific boon for consumers seeking bargains and otherwise inaccessible products, pharmacy is one online sector where the benefits are mixed. The uninitiated consumer can encounter both health and financial hazards.

From a consumer's point of view, online pharmacies seem to offer much potential value, although not necessarily on price. For housebound patients, the option of ordering medication from home and having it delivered to the door is obvious. For those living in remote areas, and consumers who are short of time and for whom reaching the pharmacy is difficult, ordering online has obvious advantages. There are also those seeking personal products who prefer anonymity.

The rewards and risks of online pharmacy shopping present a significant issue for consumer health. Two national regulatory authorities have issued detailed warnings about online pharmacies, but stopping overseas online pharmacy scams is no simple task.

The Australian Competition and Consumer Commission states there are legitimate online pharmacies that list full contact details and require valid prescriptions. However, it warns there are scams and spam emails offering medicines at very cheap prices, or without the need for prescriptions, that can cause financial and health problems.

Questions surrounding international sites selling sildenafil and other products without prescription,

Leanne Wells

Chief executive officer
Consumers Health Forum of
Australia

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COMMENT

contrary to Australian law, reflect the difficulty of ensuring the safety of overseas online pharmacies. The Therapeutic Goods Administration also warns consumers to be cautious, and points to the risk of unexpected and potentially serious adverse reactions. Given the potential for health risks for the unwary, it is concerning that there are no regulatory reviews of pharmacy sites. There is therefore a need for ongoing education by authorities on the risks of online pharmacies.

Wherever possible it is preferable for consumers to obtain their prescription medicines at a traditional pharmacy, particularly when the prescription is for a new drug or for a serious condition. Even for over-the-counter products, it is wise to buy from a pharmacy to hear of any safety advice first-hand.

The reality is that, for an increasing number of people, given population ageing and the rise in chronic illness,

online pharmacies will likely become an ever more favoured option. In Australia the online market is already dominated by well-known, presumably safe, Australian pharmacy chains.

The proliferation of online pharmacy prescription services, and now online medical consultation services, points to another dilemma that seems set to become more prevalent. That is, the growing number of remote health assessments made possible by internet and telehealth where the doctor, pharmacist or other practitioner is not seeing the patient in person. It seems that circumstances, including time and commercial pressures, are combining to make these virtual consultations ever more frequent.

The question for consumers and practitioners is how do we ensure that the overall result of the shift to virtual consultations and prescriptions will benefit our health? ◀

Letters to the Editor

Concerns about quetiapine

As a psychiatrist in private practice, I share some of the concerns about quetiapine raised by Jonathan Brett (Aust Prescr 2015;38:95-7). However, I think there is a significant role for off-label prescribing in certain patient groups. Patients with major depression, particularly those with agitation, high degrees of inner distress, or sleep difficulties often benefit substantially when quetiapine, usually 12.5–100 mg, is added to their antidepressant. The 25 mg tablet is most appropriate for this use.

If it is claimed that 'quetiapine has proven safety and efficacy when used for its approved indications', which usually entail 400–800 mg doses, I do not think further studies are needed to conclude a 25 mg dose will be safer than a 400–800 mg dose. As it is, undertreating a depressed patient's distress also carries significant risks. These risks are difficult to analyse as depressed patients who become suicidal usually get booted out of depression studies. As a result, there is a significant validity issue regarding the 'evidence' because patients who participate in depression studies differ from many of those who come through a psychiatrist's door. Indeed, those most at risk of suicide are the ones we tend to have the least evidence about to guide our management. The 'no evidence, so don't use it' mantra may well work against the welfare of many depressed patients.

Evidence is a tool, not a god, and the flaws in the evidence need to be fully understood before 'evidence' is used to formulate management guidelines.

Another area concerns personality disorders, which are difficult to treat. Psychological treatment should be the mainstay, but many patients are not very psychologically minded, and psychological treatment doesn't always work, even among those who want to change. Yet patients with personality disorders often have high levels of distress. The 'no evidence, so don't use it' mantra may again work against patient welfare, compared to the judicious use of low-dose quetiapine for such patients when they are in crisis.

Thus, quetiapine has its problems, but off-label use remains an important tool in certain clinical situations.

Alan Garrity
Psychiatrist
Dee Why, NSW

I would like to comment, as a GP, on Jonathan Brett's very timely article. I have a sizeable geriatric population in my practice, of which a fair number with evolving or full-blown dementia are in institutions. This is the area in which quetiapine use is relevant. Quetiapine 6.25–100 mg per day is very



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effective to calm patients down and help them to coexist with other institution residents or family members at home.

It goes without saying that anxiety, insomnia and depression are all looked for and treated first. Quetiapine (and other antipsychotics) are not used willy nilly. There is not much else to use and the ubiquitous benzodiazepines have a bad reputation. Risperidone at its recommended dose (by the Pharmaceutical Benefits Scheme – PBS) is often not effective enough for the agitated, noisy patient who needs to be controlled quickly. If the patient is over-sedated, family members complain and staff report hazardous falls. We respond accordingly.

Drugs used off label are written as private scripts, so PBS attempts to curtail quetiapine's use will not be effective. Non-pharmacological interventions always sound good, but for Australia's evolving institutions that have to grapple with the growing dementia population, these interventions are often disappointing in effect because qualified personnel to execute them are not easily available.

What we need are studies into quetiapine's role in these types of patients, not roadblocks against its use. If the researchers did it for risperidone, why not for quetiapine?

Peter Foenander
GP
Port Adelaide, SA

I was interested to read the June article by Jonathan Brett on the increase in prescribing of quetiapine, particularly at lower doses.

I am a GP who has contributed to those statistics due to the new phenomenon of telehealth. I work in a rural country town and have an interest in mental health and psychological medicine. I have participated in telehealth sessions with consultant psychiatrists by sitting in and providing support and follow-up. This has involved quite a lot of work with adolescents and young adults. As the GP at the consultation end of the interaction, I am providing the prescriptions recommended in the psychiatrist's management plan. The phenomenon of telehealth therefore may interfere with the statistics and information about who is prescribing quetiapine. I wonder how many other GPs are prescribing quetiapine in this way. The prescriber number statistics may not be truly reflecting the basis of these decisions.

Bronwen Howson
GP
Allora, Qld

I read with interest the article about the increasing off-label use of quetiapine. Indeed it is often used for insomnia, for example, and this is my focus. In general practice I do not see it used with personality disorders, dementia, or substance abuse, and only rarely in post-traumatic stress disorder and anxiety. That is not to say that it may not be useful in these disorders in specialised hands, but may not be indicated as prime therapy. It is nonetheless unfortunate when a medicine is denied to an individual when it suits them well, simply on the basis of esoteric and inclusion-criteria-limited epidemiological studies. The dicta of evidence-based medicine do not always serve us well in this regard.

In his article, Jonathan Brett commented that there was poor evidence for quetiapine in insomnia. He quotes one recent literature review that found only two placebo-controlled trials and concluded that the absence of safety and efficacy data precludes the use of quetiapine for insomnia.¹ Another review he quoted was from a nursing journal.² It in fact identified five studies, and three randomised controlled trials. All but one of them suggested sleep benefit from quetiapine. Two further studies reported the weight gain associated with quetiapine. The review goes on to say clinicians should consider individual patient health profiles in light of the potential weight gain with long-term quetiapine therapy.

The ascription 'off-label' seems to indicate a pejorative connotation. I would dispute this. Clinical judgement should always govern prescribing. Medication is always prescribed on balance. If the concern is sleep versus weight gain, and this seems the only concern mentioned, the lack of sleep and its deleterious effects may well transcend the appearance of weight gain. Nonetheless there seems to be more evidence in favour of usage in insomnia than was quoted.

Chris Andrews
GP
Chapel Hill, Qld

REFERENCES

1. Anderson SL, Vande Griend JP. Quetiapine for insomnia: A review of the literature. *Am J Health Syst Pharm* 2014;71:394-402.
2. Carney AC. Efficacy of quetiapine off-label uses: data synthesis. *J Psychosoc Nurs Ment Health Serv* 2013;51:11-8.

Jonathan Brett, author of the article, comments:



The mantra that no evidence of effect is not the same as evidence of no effect rings especially true for quetiapine in the era of evidence-

based medicine. For this reason quetiapine along with the other atypical antipsychotics has been identified as a priority area for research to support off-label uses.¹ The difficulties in conducting this research are well described by Dr Garrity. Exclusion criteria may limit the generalisability of a study and often patients do not neatly fall into diagnostic criteria such as those found in DSM-5. This can leave prescribers in doubt about whether findings apply to their patients.

A further complicating issue is that the risk-benefit profile of prescribing quetiapine depends upon the context in which it is prescribed. For example, the use of quetiapine to treat behavioural and psychological symptoms of dementia appears to have a poor risk-benefit profile.² Prescribing must also be considered within the context of access to alternative (predominantly psychological) management strategies. If quetiapine is being prescribed in nursing homes because non-drug interventions are not available due to lack of qualified staff,³ then the reasons for this (such as funding) should be identified and addressed rather than exposing older people to the gamut of risks that accompanies these medicines.

The nature of policy decisions to improve quality prescribing as raised by Dr Foenander is an important one. Any changes in policy should involve an understanding of the factors influencing prescribing decisions.⁴ An example given here is that the patient is unwilling to engage in psychological therapies. Another explanation may be that people are unable to access psychological therapies. Qualitative research would help give insights into patient, prescriber and systemic incentives that play a role in quetiapine prescribing. Policy decisions should ideally readjust prescribing incentives based on an understanding of prescribing decisions and engage prescribers and patients in the process rather than be a top-down authoritarian measure.

The prescriber may not be the practitioner who has recommended the treatment as in the case with telehealth. This is an important point and often missed in the absence of more in-depth review.

Regarding the use of quetiapine to treat insomnia raised by Dr Andrews, the cited review⁵ found only two randomised controlled trials including a total of 31 patients for the treatment of insomnia at baseline. The other trials identified did not include patients meeting these criteria. On balance, given

the apparent magnitude of use for insomnia and proven metabolic adverse effects at low doses,⁶ my impression is that this is a ripe area for more research. When operating in the real world where off-label use is often necessary, my feeling is that prescribers should be aware of the risk-benefit profile for this indication in this patient, the evidence gaps and the treatment alternatives. Discussing these with the patient is imperative for an informed decision to be made by the patient. Where there is significant uncertainty this should be communicated, and close monitoring with defined treatment outcomes and a strategy of treatment withdrawal are important.^{7,8} It is unclear whether this is current practice with quetiapine prescribing. Patient decision support tools may be a useful resource in this setting.⁹ An example is the NPS MedicineWise Choosing Wisely campaign that provides guidance developed by prescriber and patient stakeholders on a range of practices (including antipsychotics) with the aim of opening a dialogue between prescribers and patients in these situations.¹⁰

REFERENCES

- Walton SM, Schumock GT, Lee KV, Alexander GC, Meltzer D, Stafford RS. Prioritizing future research on off-label prescribing: results of a quantitative evaluation. *Pharmacotherapy* 2008;28:1443-52.
- Thompson Coon J, Abbott R, Rogers M, Whear R, Pearson S, Lang I, et al. Interventions to reduce inappropriate prescribing of antipsychotic medications in people with dementia resident in care homes: a systematic review. *J Am Med Dir Assoc* 2014;15:706-18.
- Gerhard T, Lucas J, Crystal S. Abstract 160: Association between nursing home staffing levels and off-label use of antipsychotics. *Pharmacoepidemiol Drug Saf* 2008;17 Suppl 1:S1-294.
- Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458-65.
- Anderson SL, Vande Griend JP. Quetiapine for insomnia: A review of the literature. *Am J Health Syst Pharm* 2014;71:394-402.
- Cates ME, Jackson CW, Feldman JM, Stimmel AE, Woolley TW. Metabolic consequences of using low-dose quetiapine for insomnia in psychiatric patients. *Community Ment Health J* 2009;45:251-4.
- Gazarian M, Kelly M, McPhee JR, Graudins LV, Ward RL, Campbell TJ. Off-label use of medicines: consensus recommendations for evaluating appropriateness. *Med J Aust* 2006;185:544-8.
- Council of Australian Therapeutic Advisory Groups. Rethinking medicines decision-making in Australian hospitals: guiding principles for the quality use of off-label medicines. Sydney: CATAG; 2013.
- Walsh T, Barr PJ, Thompson R, Ozanne E, O'Neill C, Elwyn G. Undetermined impact of patient decision support interventions on healthcare costs and savings: systematic review. *BMJ* 2014;348:g188.
- Choosing Wisely Australia, an initiative of NPS MedicineWise. Sydney: NPS MedicineWise; 2015. www.choosingwisely.org.au [cited 2015 Nov 4]

Treating hepatitis C – what's new?

SUMMARY

Chronic hepatitis C infection causes cirrhosis, liver failure and hepatocellular carcinoma, and is the most common indication for liver transplantation.

Hepatitis C is curable and complications can be prevented. Until recently, treatment regimens involved peginterferon alfa. Although effective, their widespread use is limited by treatment-related toxicity.

A number of direct-acting drugs for hepatitis C, such as sofosbuvir, have recently been developed and target multiple steps in the viral life cycle. These drugs are used in combination in interferon-free regimens. Short courses are highly effective with minimal toxicity.

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Introduction

It is estimated that more than 230 000 Australians are chronically infected with the hepatitis C virus.¹ The disease slowly progresses over decades. A significant minority of patients will develop cirrhosis (5–20% after 20 years) and be at risk of complications including liver failure and hepatocellular carcinoma.^{2–4} Hepatitis C is the most common indication for liver transplantation in Australia. These complications may be prevented by viral eradication.

There are six main genotypes of hepatitis C virus – genotypes 1–6. Each of these can be further subdivided (e.g. 1a, 1b). Current Pharmaceutical Benefits Scheme (PBS)-subsidised treatment involves the combination of peginterferon alfa and ribavirin for all genotypes except genotype 1. First-line therapy for genotype 1 disease is triple therapy with peginterferon, ribavirin and a viral protease inhibitor. Overall cure rates are above 70%. However, many patients are ineligible for peginterferon or intolerant due to treatment-related toxicity.⁵

In 2015, several peginterferon-free treatments have been approved by the Therapeutic Goods Administration (TGA). They are simple, short regimens with high cure rates and minimal toxicity, and have received positive recommendations from the Pharmaceutical Benefits Advisory Committee (PBAC). They are currently being considered for PBS listing.

Diagnosis and assessment

Most patients with chronic hepatitis C are asymptomatic. Transmission of the virus is associated with identifiable risk factors, and most diagnoses result from screening at-risk individuals (see Box).

Testing for infection

The appropriate screening test for hepatitis C infection involves detection of specific antibodies to the virus in the blood. Their presence indicates exposure to hepatitis C virus from a current or past infection. Current infection is identified using a qualitative polymerase chain reaction (PCR) assay to detect viral RNA.

Approximately 25% of people with acute hepatitis C infection will clear it spontaneously within six months. These individuals continue to have anti-hepatitis C antibodies (positive screening test), but do not have detectable viral RNA in plasma (negative PCR test). In patients with recent exposure to hepatitis C virus, the

Key words

asunaprevir, daclatasvir,
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protease inhibitors, ribavirin,
sofosbuvir

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CPD
FOR PHARMACISTS

This article has a continuing professional development activity for pharmacists available at www.australianprescriber.com/continuing-professional-development

Box Populations at increased risk of hepatitis C infection

People who inject drugs or have done so in the past
Sex workers
People in custodial settings
People with tattoos or body piercings
People who received a blood transfusion/organ transplant before 1990
Children born to mothers with hepatitis C
Sexual partners of people with hepatitis C
People with HIV or hepatitis B
People with liver disease (persistently elevated alanine aminotransferase)
People who have had a needle-stick injury
Migrants from high-prevalence regions (Egypt, Pakistan, Mediterranean and Eastern Europe, Africa and Southern Asia)

ARTICLE

Treating hepatitis C

PCR test should be repeated after six months. There is no current recommendation for how frequently high-risk individuals should be screened, but annual serology is reasonable.

Assessing for liver disease

Once a patient has chronic infection, further investigation (Table 1) should assess the stage of liver disease. It is important to know whether a patient has advanced liver disease to determine the urgency for treatment, and also to screen for complications of cirrhosis such as portal hypertension and hepatocellular carcinoma.

Risk factors for cirrhosis include:

- male gender
- older age at infection
- prolonged duration of infection (>20 years)
- comorbidities including excessive alcohol consumption, diabetes and metabolic syndrome
- coinfection with hepatitis B or HIV.

Clues to the presence of advanced liver disease include peripheral stigmata of chronic liver disease

(e.g. leuconychia, spider naevi), splenomegaly and thrombocytopenia. Low albumin, raised bilirubin and raised INR are markers of reduced liver function and may reflect advanced liver disease.

All patients should have a liver ultrasound to examine for features of portal hypertension (e.g. splenomegaly, reversal of portal vein flow), and to screen for hepatocellular carcinoma. Transient elastography (FibroScan) is a non-invasive ultrasonic technique for measuring liver stiffness as a marker of the stage of liver fibrosis. It is widely available in specialist centres. A key question is what threshold of liver stiffness should be used to define cirrhosis, as this has implications for treatment duration. Thresholds have varied across clinical trials evaluating different regimens,^{6,7} but a reasonable threshold for treatment decision making is 12.5 kPa. Serum biomarkers for liver fibrosis have also been developed, but are not currently reimbursed.

Liver biopsy is generally reserved for patients when there is a diagnostic query. Liver histology is no longer required for accessing antiviral therapy.

Table 1 Diagnostic work-up for hepatitis C

Diagnosis	Comment
Hepatitis C antibody positive (serology)	Indicates exposure to hepatitis C virus (past/current infection)
Hepatitis C viral RNA positive (qualitative PCR)	Indicates current infection
Post-diagnosis	
Hepatitis C genotype	Treatment regimens are genotype specific
Hepatitis C viral RNA level (quantitative PCR)	Predicts interferon responsiveness Establishes baseline for comparison once treatment has started
Full blood examination	Thrombocytopenia suggests portal hypertension
Markers of liver functional reserve: • liver function tests • INR	Low albumin, raised bilirubin and raised INR all suggest advanced liver disease
Liver ultrasound	Identify portal hypertension, screen for hepatocellular carcinoma
Hepatitis A, B serology, HIV serology	Important co-infections
Specialist	
Host IL28B genotype*	Predicts interferon responsiveness
Transient elastography* (FibroScan)/serum fibrosis biomarker (e.g. HepaScore, FibroTest, ELF test)	Non-invasive markers of liver fibrosis stage
± Liver biopsy	Infrequently performed No longer a requirement for treatment

PCR polymerase chain reaction

Alfa fetoprotein testing is no longer recommended as part of hepatitis C screening.

* Neither IL28B genotyping nor transient elastography are currently reimbursed. Both tests are widely available at specialist centres.

Viral genotyping

Approved treatment regimens for hepatitis C are genotype specific (Table 2). It is therefore important to find out which viral genotype the patient has in order to determine the most appropriate therapy. The common genotypes in Australia are genotype 1 (54%) and genotype 3 (37%).⁸

Other investigations

Before initiating antiviral therapy, the amount of viral RNA should be quantified by PCR. Testing the host IL28B genotype is also useful (Table 1).^{9,10} Both of these predict a patient's response to peginterferon plus ribavirin therapy, particularly for genotype 1 infection.

Referral to a specialist

All patients with chronic hepatitis C should be considered for antiviral therapy and referred to a clinician with a specialist interest. Patients with clinical evidence of cirrhosis are the highest priority for referral.

Treatments for hepatitis C

The goal of treatment is a virological cure (sustained virological response). This is defined as undetectable viral RNA in plasma 24 weeks after treatment has finished. A sustained virological response prevents the development of cirrhosis. In patients who already have cirrhosis, a sustained virological response reduces the risks of liver failure and hepatocellular carcinoma.

The approved treatment combinations for hepatitis C in Australia are summarised in Tables 2 and 3.

Currently, all PBS-subsidised regimens involve peginterferon plus ribavirin.

The widespread use of peginterferon-containing regimens has been limited by treatment-related toxicity, as well as disappointing efficacy in patients with advanced liver disease. Direct-acting antiviral drugs targeting multiple steps in the viral life cycle have been developed and used in combination to successfully treat hepatitis C infection. These interferon-free regimens have very high efficacy, short duration (8–12 weeks) and minimal toxicity. They are suitable for patients who

Table 2 TGA-approved interferon-containing regimens for hepatitis C

Viral genotype	Treatment regimen	Treatment duration	Response rates ^{† ‡}
1	Simeprevir + peginterferon + ribavirin	24–48 weeks [§]	>70%
	Telaprevir + peginterferon + ribavirin	24–48 weeks [§]	>70%
	Boceprevir + peginterferon + ribavirin	24–48 weeks [§]	>70%
	Asunaprevir + daclatasvir + peginterferon + ribavirin*	24 weeks	>90%
	Sofosbuvir + peginterferon + ribavirin*	12 weeks	90%
2 and 3	Peginterferon + ribavirin	24 weeks	>70%
	Sofosbuvir + peginterferon + ribavirin*	12 weeks	90%
4	Peginterferon + ribavirin	48 weeks	40–50%
	Simeprevir + peginterferon + ribavirin	24–48 weeks [§]	>70%
	Asunaprevir + daclatasvir + peginterferon + ribavirin*	24 weeks	>90%
	Sofosbuvir + peginterferon + ribavirin*	12 weeks	90%#
6	Peginterferon + ribavirin	48 weeks	70–80%
	Sofosbuvir + peginterferon + ribavirin*	12 weeks	>90%

TGA Therapeutic Goods Administration

* Not listed on the Pharmaceutical Benefits Scheme at the time of writing.

[†] Response rate was defined as proportion of patients with a sustained virological response (undetectable viral RNA in serum) measured at 3 or 6 months after the end of treatment. Results reflect the minimum overall response rate in published studies including non-cirrhotic and cirrhotic patients.

[‡] Response rates were lower in patients with cirrhosis.

[§] Response-guided therapy for protease inhibitors: treatment-naïve patients, and previous relapsers following peginterferon + ribavirin, are eligible for shorter treatment duration if serum viral RNA concentrations are undetectable after 4 weeks of treatment. Previous partial or null responders are not eligible for short-duration therapy. (Note: Previous relapsers are patients who had undetectable viral RNA concentrations following interferon-based therapy and detectable viral RNA during follow-up. Previous partial responders are patients with previous on-treatment $\geq 2 \log_{10}$ IU/mL reduction in viral RNA from baseline at week 12 and detectable RNA at the end of previous therapy with peginterferon + ribavirin. Previous null responders are patients with previous on-treatment $< 2 \log_{10}$ reduction in RNA from baseline at week 12 or $< 1 \log_{10}$ reduction in RNA from baseline at week 4 during previous peginterferon + ribavirin therapy.)

The efficacy of sofosbuvir + peginterferon + ribavirin in patients who have previously been non-responders to peginterferon + ribavirin is not known.

Table 3 TGA-approved interferon-free regimens for hepatitis C

Viral genotype	Treatment regimen*	Patient characteristics			Response rates†
		No cirrhosis	Cirrhosis	Cirrhosis + treatment-experienced	
1a/b	Sofosbuvir + ledipasvir	12 weeks‡	12 weeks	24 weeks§	≥95%
1a	Paritaprevir + ritonavir + ombitasvir + dasabuvir	12 weeks + ribavirin	12 weeks + ribavirin	12 weeks + ribavirin#	≥95%
1b		12 weeks	12 weeks + ribavirin¶	12 weeks + ribavirin¶	
1a/b	Sofosbuvir + daclatasvir ± ribavirin	12 weeks	12 weeks + ribavirin OR 24 weeks**	12 weeks + ribavirin OR 24 weeks** ††	≥95%
1b	Asunaprevir + daclatasvir	24 weeks	24 weeks	24 weeks	90%
2	Sofosbuvir + ribavirin	12 weeks	12 weeks‡‡	12 weeks‡‡	F0-3 >90% F4 >80%
3	Sofosbuvir + ribavirin	24 weeks	24 weeks	24 weeks	F0-3 >80% F4 62-82%§§
3	Sofosbuvir + daclatasvir ± ribavirin	12 weeks	12 weeks + ribavirin OR 24 weeks##	12 weeks + ribavirin OR 24 weeks##	F0-3 >90% F4 >80%##

TGA Therapeutic Goods Administration F0-3 METAVIR fibrosis stage 0-3 F4 METAVIR fibrosis stage 4 (cirrhosis)

* Not listed on the Pharmaceutical Benefits Scheme at the time of writing.

† Response rate was defined as proportion of patients with a sustained virological response (undetectable viral RNA in serum) measured at 3 or 6 months after the end of treatment.

‡ 8 weeks may be considered in treatment-naïve patients with no cirrhosis and a baseline viral RNA concentration $<6 \times 10^6$ IU/mL.

§ 24 weeks is recommended for patients who have failed treatment with peginterferon + ribavirin with or without a protease inhibitor.

24 weeks is recommended for patients who have had a previous null response to peginterferon + ribavirin, defined by a decrease in the viral RNA level of $<2 \log_{10}$ IU/mL at week 12 or $<1 \log_{10}$ IU/mL at week 4 during previous peginterferon + ribavirin treatment.

¶ Recent data suggest that ribavirin may not be necessary for patients with genotype 1b disease and cirrhosis.

** In patients with genotype 1 disease and cirrhosis, consider adding ribavirin to the sofosbuvir + daclatasvir 12-week regimen, or prolonging treatment duration to 24 weeks.

†† In patients with genotype 1 disease who have failed protease-based triple therapy, prolonging treatment to 24 weeks is recommended.

‡‡ In patients with genotype 2 disease and cirrhosis, consider prolonging treatment to 16–24 weeks.¹¹

§§ Response rates are over 80% in all genotype 3 subgroups except treatment-experienced patients with cirrhosis (reported at 62–77%).^{12,13}

In patients with genotype 3 disease and cirrhosis, consider adding ribavirin to the 12-week regimen, or prolonging treatment duration to 24 weeks. In a single phase III study evaluating 12 weeks of sofosbuvir + daclatasvir with no ribavirin, response rates were 96% in patients with no cirrhosis vs 63% in patients with cirrhosis.¹⁴ The efficacy of sofosbuvir + daclatasvir + ribavirin for 12 or 16 weeks in patients with genotype 3 and cirrhosis is currently being evaluated. Preliminary data suggest response rates >85% in genotype 3 patients with cirrhosis who are treated with sofosbuvir + daclatasvir for 24 weeks.¹⁵

cannot tolerate interferon combinations or who are ineligible. These patients previously had no treatment options. The PBAC has recently made positive recommendations to list these regimens on the PBS.

Interferon-containing regimens

The combination of subcutaneous peginterferon plus oral ribavirin has been the backbone of treatment for hepatitis for the past decade.

Genotype 2 and 3 hepatitis C is treated with peginterferon plus ribavirin for 24 weeks (Table 2). Response rates are over 70%, but are lower in patients with cirrhosis.

Protease inhibitors

Treatment regimens for genotype 1 infection can include a protease inhibitor such as simeprevir, telaprevir or boceprevir (Table 2).

Simeprevir was approved in late 2014 and is now the first-line protease inhibitor for genotype 1 infections. It is also approved for genotype 4 infections. Compared to telaprevir or boceprevir, it offers the benefit of a single daily dose and an improved toxicity profile. Also, the majority of patients will qualify for shorter duration therapy (24 vs 48 weeks). Treatment-naïve patients are eligible for short-duration therapy if they have undetectable viral RNA at week four of treatment (Table 2).

In patients with genotype 1 infection, triple therapy with a protease inhibitor has been associated with response rates of over 70%. However, some patient subgroups remain harder to cure, including those with cirrhosis, and those who have previously failed treatment with peginterferon plus ribavirin. Cure rates are less than 50% in these patients.

A fourth protease inhibitor, asunaprevir, has been approved by the TGA in combination with daclatasvir (an inhibitor of the nonstructural protein NS5A). This is a quadruple therapy regimen with peginterferon and ribavirin for genotype 1 (and genotype 4) infections (Table 2). It has not yet been listed on the PBS.

Sofosbuvir

More recently, sofosbuvir, an NS5B nucleotide polymerase inhibitor, has been approved for use by the TGA but is not yet listed on the PBS. For patients with genotypes 1, 4, 5 or 6, sofosbuvir plus peginterferon and ribavirin for 12 weeks is associated with response rates of approximately 90%. Response rates among patients with cirrhosis are 80%.

For genotype 3 infections, sofosbuvir can be added to peginterferon and ribavirin in a 12-week regimen or to ribavirin alone in a 24-week regimen. The response rate for 12 weeks of triple therapy was higher than for 24 weeks of sofosbuvir plus ribavirin (93% vs 84%).¹² For genotype 2 infections, sofosbuvir without ribavirin for 12 weeks is associated with response rates over 90%.

Interferon-free regimens

Multiple interferon-free treatment regimens have recently been approved for genotype 1, 2 and 3 hepatitis C infections (Table 3). The first-line regimens for genotype 1 include:

- sofosbuvir and ledipasvir (an NS5A inhibitor)^{6,7}
- paritaprevir (a protease inhibitor that requires ritonavir boosting), ombitasvir (NS5A inhibitor) and dasabuvir (NS5B polymerase non-nucleoside inhibitor) with or without ribavirin.¹⁶⁻¹⁸

For both regimens, response rates are over 95% across all patient groups including those with cirrhosis and those who have previously failed on peginterferon plus ribavirin. Treatment duration is 12 weeks for most patients. The pill burden is low and the regimens are well tolerated.

A third regimen, sofosbuvir plus daclatasvir, was very effective in a phase II study of patients with genotype 1 infection who had previously failed protease inhibitor-based triple therapy.

Interferon-free treatment regimens for genotype 3 infection include sofosbuvir plus ribavirin for 24 weeks, and the combination of sofosbuvir plus daclatasvir for 12 weeks¹²⁻¹⁴ (Table 3). These regimens are very effective in patients who do not have cirrhosis.

Genotype 3 remains harder to cure in patients with cirrhosis, particularly in those who have previously failed peginterferon and ribavirin. In this subgroup,

triple therapy with sofosbuvir plus peginterferon and ribavirin for 12 weeks produces better response rates than sofosbuvir plus ribavirin for 24 weeks. A prospective study is evaluating the benefit of adding ribavirin to the 12-week regimen of sofosbuvir plus daclatasvir versus prolonging treatment duration of sofosbuvir plus daclatasvir. Preliminary data from an early-access program in Europe suggest that sustained virological response rates are over 85% among cirrhotic patients treated with sofosbuvir plus daclatasvir for 24 weeks.¹⁵

The approved interferon-free treatment regimen for genotype 2 infection is sofosbuvir plus ribavirin for 12 weeks (Table 3). The combination of sofosbuvir plus ledipasvir is effective for genotype 4 and 6 infections. Paritaprevir/ritonavir plus ombitasvir plus ribavirin is effective for genotype 4 infections.

Adverse reactions

Adverse reactions to hepatitis C treatments can be a problem. Interferon-based regimens are associated with considerable morbidity, and many patients are intolerant to or ineligible for peginterferon. Intensive monitoring is required during treatment. In contrast, interferon-free regimens are well tolerated with fewer adverse effects and very low discontinuation rates.

Interferon-based regimens

The most common adverse effects of peginterferon include systemic symptoms (flu-like illness with fevers, lethargy and myalgias), fatigue, bone marrow suppression, mood disturbance (irritability, depressed mood, insomnia) and alopecia. Severe cytopenias, major depression and psychosis occur less frequently. Peginterferon should be used with caution in patients with a history of depression. Untreated major depression or psychosis is a contraindication to therapy.

Autoimmune complications are uncommon and include thyroid disturbance and exacerbation of psoriatic and rheumatoid arthritis. Interferon-based regimens may precipitate hepatic decompensation in patients with advanced liver disease. Treatment may be contraindicated and should only be considered within a specialised hepatitis C centre. Patients with a platelet count below $100 \times 10^9/L$ and albumin below 35 g/L have been identified as a high-risk population.

Ribavirin

Ribavirin commonly causes haemolytic anaemia, which may precipitate or exacerbate symptoms of ischaemic heart disease. Dose reduction may be necessary. Although erythropoietin may be used to maintain haemoglobin concentrations during ribavirin therapy, it is not PBS-listed for this indication.

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Ribavirin is teratogenic so is contraindicated in pregnancy. Two forms of contraception are recommended for men and women during treatment and for six months afterwards.

Ribavirin is renally excreted so dose reduction is required in patients with significant renal impairment. Treatment should occur in a specialist centre.

Protease inhibitors

The protease inhibitors present new challenges, with additional adverse effects and drug-drug interactions.¹⁹⁻²² Telaprevir and boceprevir both need to be taken three times a day, and are associated with anaemia and gastrointestinal disturbance.

Telaprevir is commonly associated with a rash, which may be severe and life-threatening. Simeprevir has largely replaced telaprevir and boceprevir for use with peginterferon plus ribavirin for genotype 1 infections. It seems to have better tolerability^{11,23} and only needs to be taken once a day. Common adverse effects are mild and include photosensitivity and transient hyperbilirubinaemia due to inhibition of bilirubin transporters.

Interferon-free regimens

The most common adverse effects with sofosbuvir plus ledipasvir are mild fatigue, headache, nausea and insomnia. This combination is safe and effective even in patients with decompensated liver disease. Sofosbuvir is not recommended in combination with amiodarone as symptomatic bradycardia has been reported. Sofosbuvir is renally excreted and should not be used in patients with an estimated glomerular filtration rate below 30 mL/min pending further studies.

The combination of paritaprevir/ritonavir, ombitasvir and dasabuvir is also well tolerated. Paritaprevir causes a transient hyperbilirubinaemia due to inhibition of biliary transporters. Approximately 1% of patients in the phase III clinical trials experienced increases in serum alanine aminotransferases. This was most common in women taking concomitant ethinyloestradiol. It is recommended that ethinyloestradiol-containing drugs are stopped before starting treatment.

Studies are currently evaluating the safety of paritaprevir/ritonavir, ombitasvir and dasabuvir in patients with decompensated liver disease. Patients with decompensated liver disease should not be treated with this regimen until there are more data.

Pregnancy

There are no safety data for interferon-free regimens in pregnancy. Ribavirin is contraindicated in pregnancy and requires contraceptive precautions.

Drug interactions

Drug-drug interactions may occur with all interferon-free treatment regimens, and relevant drugs include proton pump inhibitors, statins and common antibiotics. Concomitant medicines should be reviewed before starting any patient on treatment. An independent resource is available from the University of Liverpool (www.hep-druginteractions.org).

Treat now or wait?

In the context of such dramatic therapeutic developments, it is important for clinicians and patients to decide whether to pursue treatment now with current PBS-subsidised regimens, or to defer treatment until interferon-free regimens become available. Combinations listed in Table 3 have been recommended by the PBAC, but PBS listing has not been confirmed. In light of this, we currently advocate for treatment deferral with monitoring every six months.

Post-treatment care

Patients with early-stage fibrosis who achieve a sustained viral response do not require long-term follow-up. They should be advised that hepatitis C serology tests will remain positive, but that it is not protective and repeat exposure may lead to reinfection.

Patients with cirrhosis do need to remain in long-term follow-up to monitor for complications including portal hypertension and hepatocellular carcinoma. This is best coordinated by a gastroenterologist. Patients with comorbid liver disease, such as non-alcoholic steatohepatitis, will also require specific management.

Treatment of hepatitis C in the future – new models of care

Treatment of hepatitis C currently occurs in specialist liver clinics, typically within tertiary hospitals. This system is very effective and necessary to manage the complexities of interferon-based treatment. However, capacity is limited. Patients with advanced fibrosis and cirrhosis will need to remain in the tertiary system for management of their liver disease. However, patients who do not have cirrhosis may not need to be managed in a specialist clinic if they can be treated with simple interferon-free regimens. This will allow new models of care involving GPs, nurse practitioners, opioid-substitution therapy clinics and the custodial system. The PBAC has recommended that newer hepatitis C therapies are listed on the general schedule to promote treatment in primary care.

Conclusion

The clinical complications of hepatitis C can be prevented by viral eradication. All patients should be considered for treatment and actively engaged in care. Current subsidised regimens continue to include peginterferon. Although their efficacy is good, the associated toxicity means that only a minority of patients start antiviral therapy.

The introduction of interferon-free therapies in the near future will increase treatment efficacy, tolerability and uptake. These regimens will play a front-line role

in tackling the hepatitis C epidemic, with expanded models of care as well as treatment prevention programs to reduce transmission. ◀

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REFERENCES

1. Sievert W, Razavi H, Estes C, Thompson AJ, Zekry A, Roberts SK, et al. Enhanced antiviral treatment efficacy and uptake in preventing the rising burden of hepatitis C-related liver disease and costs in Australia. *J Gastroenterol Hepatol* 2014;29 Suppl 1:1-9.
2. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997;349:825-32.
3. Seeff LB. Natural history of chronic hepatitis C. *Hepatology* 2002;36 Suppl 1:S35-46.
4. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA* 2000;284:450-6.
5. Grebely J, Bryant J, Hull P, Hopwood M, Lavis Y, Dore GJ, et al. Factors associated with specialist assessment and treatment for hepatitis C virus infection in New South Wales, Australia. *J Viral Hepat* 2011;18:e104-16.
6. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al.; ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014;370:1483-93.
7. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al.; ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014;370:1889-98.
8. Bowden DS, Berzsényi MD. Chronic hepatitis C virus infection: genotyping and its clinical role. *Future Microbiol* 2006;1:103-12.
9. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009;461:399-401.
10. Thompson AJ, Muir AJ, Sulkowski MS, Ge D, Fellay J, Shianna KV, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. *Gastroenterology* 2010;139:120-9.e18.
11. European Association for Study of Liver. EASL recommendations on treatment of hepatitis C 2015. *J Hepatol* 2015;63:199-236.
12. Foster GR, Pianko S, Cooper C, Brown A, Forton D, Nahass RG, et al. Sofosbuvir plus Peg-IFN/RBV for 12 weeks vs sofosbuvir/RBV for 16 or 24 weeks in genotype 3 HCV-infected patients and treatment-experienced cirrhotic patients with genotype 2 HCV: The BOSON Study. *J Hepatol* 2015;62 Suppl 2:S259-60.
13. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al.; VALENCE Investigators. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014;370:1993-2001.
14. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al.; ALLY-3 Study Team. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology* 2015;61:1127-35.
15. Hezode C, De Ledinghen V, Fontaine H, Zoulim F, Lebray P, Boyer N, et al. Daclatasvir plus sofosbuvir with or without ribavirin in patients with HCV genotype 3 infection: interim analysis of a French multicenter compassionate use program. *J Hepatol* 2015;62 Suppl 2:S265-6.
16. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370:1594-603.
17. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourlière M, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370:1604-14.
18. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014;370:1973-82.
19. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al.; SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1195-206.
20. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al.; HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1207-17.
21. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al.; ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011;364:2405-16.
22. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al.; REALIZE Study Team. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011;364:2417-28.
23. 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* 2015;22:366-75.

ARTICLE

Opioid prescribing pitfalls: medicolegal and regulatory issues

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Inappropriate opioid prescribing can lead to patient harm as well as a medicolegal risk to prescribers.

Prescribers need to be familiar with the indications, contraindications and harms associated with opioids.

When prescribing opioids, doctors must be aware of their clinical, ethical and legal responsibilities, particularly the legislative requirements in their state. Failure to comply with these can result in disciplinary action.

To avoid potential conflict with differing state regulations on opioid prescribing, doctors should advise patients to get their prescription dispensed in the same state in which it was written.

Key wordsdrug regulation, opioids,
pain management*Aust Prescr 2015;38:198-203**First published online
2 September 2015***Introduction**

In June 2014, a New South Wales deputy state coroner handed down findings into the deaths of three young patients in Sydney.¹ The coroner found that prescription drugs, some of which were opioids, caused or contributed to these unintentional deaths. The inquest highlighted examples of the difficulties in dealing with doctor-shopping behaviour, and involved hearing evidence from numerous practitioners who were often concurrently involved in the care of these patients.

More recently in December 2014, a Victorian coroner delivered findings into the death of a 38-year-old man with a long history of mental illness.² The man died of pneumonia in the setting of methadone and benzodiazepine use. The coroner found that the deceased received care and prescriptions from two GPs who had never met or spoken to each other about him. This reveals the difficulties and challenges of sharing prescribing information between doctors and practices.²

In their published findings, both of these coroners, along with others around the country, have recommended reforms to the way opioids are regulated, monitored and prescribed.

Opioid use in Australia

The use of opioids in acute pain and malignant disease is rarely in dispute. In contrast, their use for chronic non-malignant pain is controversial and there is limited evidence to justify the long-term use of opioids for this indication. This is partly due to the difficulty of conducting trials in patients with such heterogeneous conditions.^{3,4} The evidence is often based on highly selected patients with minimal comorbidities, and

placebo is used as the comparator rather than other pain control measures.^{3,4} Population studies are not supportive of a good outcome for patients, but are often criticised because they are unable to show a causative link between opioids and overall health outcomes.

The prescription and consumption of opioids have markedly increased in Australia.⁵ In the 20 years to 2012, there was a 15-fold increase in the number of opioid prescriptions dispensed.⁶ In 2013 in Australia, there were 12 different opioids available in 241 formulations. Opioid use in Australia is high, particularly oxycodone and morphine,⁶ but it is nowhere near the epidemic proportions seen in the USA.^{7,8}

An editorial examining some of the reasons for the explosive increase in the use of opioids in the USA describes a paradigm shift in the treatment of pain.⁷ The author states that 'In contemporary medical culture, self-reports of pain are above question, and the treatment of pain is held up as the holy grail of compassionate medical care.'

Not all opioid prescribing is for chronic pain. An Australian analysis of 4666 GP encounters found that 3.5% of opioids were prescribed for malignant neoplasm, 43.9% for chronic pain, and the remainder for non-chronic pain and other causes.^{5,9} Nevertheless, there has been increasing concern surrounding the volume of opioids used for chronic non-malignant pain and associated harms. The need for vigilance has been highlighted.^{3,9} Illicit diversion of opioids, which mirrors the increase in their prescription, is also of concern.⁸

The Pain and Opioids IN Treatment study¹⁰ supports concern that opioids may impede patients getting

back to work, or do not help.¹¹ The study found that approximately two-thirds of patients treated with opioids are unemployed or receiving government benefits. This has prompted calls for practitioners to re-examine the goals of opioid therapy in patients.¹¹

Harm from opioids

Adverse events associated with opioid use have been well documented.^{3,12} Hospitalisations and deaths in which opioids have been a contributing factor are increasing.⁶ As highlighted by the Coroners Court of Victoria, 82.8% of drug-related deaths in Victoria were due to prescription drugs.¹³ The top contributing medicines were opioids and benzodiazepines.

The importance of regulation

The regulation of opioids is a public health issue.¹⁴ The National Poisons Standard¹⁵ sets out the scheduling of all poisons in accordance with the degree of individual risk, and the risk to public health and safety.¹⁴ Each state and territory in Australia has the power to impose statutory control over the supply, access, record keeping, administration and disposal of all medicines and poisons.¹⁴ Each state also has a system of monitoring the dispensing of opioids. However, they vary in their capability and scope of monitoring. Only Tasmania has a real-time dispensing monitoring system, referred to as Electronic Recording and Reporting of Controlled Drugs (ERRCD).

In writing a prescription for an opioid, doctors have a clinical, ethical and legal responsibility. The importance of abiding by the laws and regulations that govern prescribing cannot be understated. Doctors who disregard their responsibility risk being the subject of civil, disciplinary or coronial proceedings.

A review of 32 Victorian and NSW disciplinary decisions involving opioid prescribing between 2010 and 2014 has been reported. It found the practitioners were all GPs who were guilty of inappropriate prescribing of Schedule 8 or Schedule 4 drugs. The decisions all involved failure to keep adequate records and mostly involved inappropriate prescribing to multiple patients. However, three GPs had each prescribed to only one patient.¹⁶ All of the doctors had conditions placed on their practice, and some were suspended or de-registered. Sanctions ranged from a caution through to a reprimand.¹⁶

Responsible and lawful prescribing

Treating patients with chronic non-malignant pain is always challenging. In addition to medicolegal considerations, all prescribers should consider and balance what is in the best interests of their patient (see Fig.). Opioids, which may have a role to play in some patients' management, should be prescribed

in accordance with established guidelines and good clinical practice. In order to prescribe opioids safely, effectively, responsibly and lawfully, we recommend that GPs address a number of sequential questions.

Are opioids an appropriate choice?

To address this question, it is necessary to consider patient-specific factors that contribute to a doctor's clinical decision making including:^{3,12,17,18}

- Should opioids be prescribed at all?
- Have all non-pharmacological options of management been considered?
- Is there a plan of management in place?
- Have the goals of treatment been defined?
- Have all of the psychosocial factors been considered?
- Is the patient at risk of dependence?
- Are there potential drug interactions?
- Have the maximum dose and exit strategy been defined?

Before and after commencing an initial trial period of opioids, a comprehensive assessment should be performed.¹⁹

Are the clinical indication, dose, frequency, repeats and management plan clearly documented?

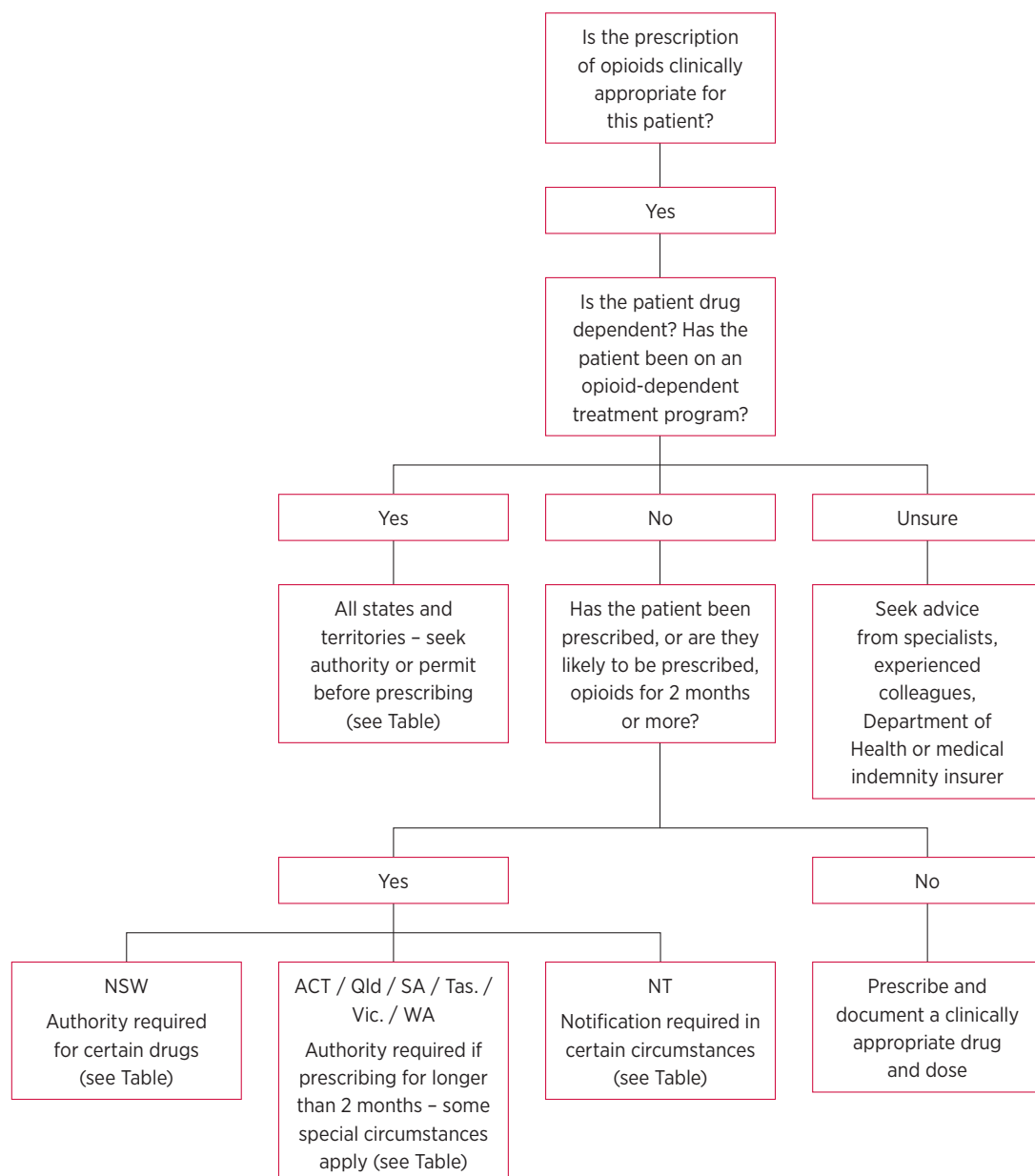
Clear, complete and adequate medical records are good clinical practice and reduce medicolegal risk. In some states, such as NSW, they are a statutory requirement.²⁰ Medical records are also a requirement of the Medical Board of Australia's Code of Conduct.²¹

Is an authority from the state-based pharmaceutical services unit required in addition to any PBS authority?

Many prescribers are not aware that an authority from the Pharmaceutical Benefits Scheme (PBS) is not the same as seeking an authority, or a permit, from the state-based pharmaceutical services unit or equivalent.

A sound understanding of the legislative definition of drug dependence is crucial. A prescriber must use clinical judgment to determine whether the patient is drug dependent in accordance with the legislative definition. The definition varies between states (see Table), but usually relates to the patient's behaviour (drug seeking or otherwise) rather than the medical definition of drug dependence which traditionally refers to physical dependence.¹⁴ In many patients, this is not a simple task. Various coroners have noted that prescribers are often limited in their ability to identify such behaviour by systemic issues such as the absence of real-time prescription monitoring.

Fig. Guide to the steps required to lawfully prescribe opioids



It is crucial that all prescribers are aware of and comply with the legislative requirements (see Table). Although these differ from state to state, GPs should be aware of the following:

- If a GP knows (or ought to know) that a patient is drug dependent, an authority or permit must be sought (Table). This applies equally in circumstances where a patient who is on opioids starts to exhibit behaviour that would reasonably lead the GP to conclude that the patient is drug dependent. Furthermore, special consideration needs to be given to patients who are (or have been) on opioid treatment programs, as some states consider these patients as drug dependent.
- If the patient is not drug dependent, in most states (except NSW) the prescriber must notify or apply for a permit or authority if the patient has been treated with opioids (by any doctor) for longer than two months (see Table).
- In NSW, all injectable opioids, and some oral opioids (such as buprenorphine, methadone and hydromorphone), require an authority to be prescribed for longer than two months. The other opioids do not require an authority.
- In some states (such as Qld), rules for notification or permits apply for some Schedule 4 drugs of dependence, such as benzodiazepines.

- Advice on whether an authority or permit is required can be sought from the relevant state-based authority.

Failure to apply for a permit or authority is the most common allegation brought against GPs who find themselves the subject of disciplinary proceedings.

Interstate prescriptions

The movement of patients (and GPs) across state borders is not uncommon. It is therefore important to be aware of legislative restrictions that apply in the state where the prescription is dispensed (see Table next page). Generally, the prescribing doctor must act in accordance with the regulations that apply in that state. These regulations differ in each state, and are not the same as the regulations of the PBS. This is a particular issue for doctors working in towns close to state borders. To avoid any potential conflict with state regulations, doctors should advise the patient that prescriptions should be dispensed in the state in which the prescription is written.

REFERENCES

1. Inquest into the Deaths of Christopher Salib, Nathan Attard and Shamsad Akhtar. Findings of Deputy State Coroner C Forbes, 21 June 2014. Sydney: State Coroners Court of New South Wales; 2014.
www.coroners.justice.nsw.gov.au/Documents/doctor%20shopping%20amended%20finding.pdf [cited 2015 Aug 12]
2. Finding - Inquest into the Death of Paul Kanis. Finding of Coroner Heffey, 17 December 2014. Melbourne: Coroners Court of Victoria; 2014.
www.coronerscourt.vic.gov.au/home/coroners+written+findings/findings+-+inquest+into+the+death+of+paul+kanis [cited 2015 Aug 12]
3. Prescription Opioid Policy: Improving management of chronic non-malignant pain and prevention of problems associated with prescription opioid use. Sydney: Royal Australasian College of Physicians; 2009.
www.racp.edu.au/docs/default-source/advocacy-library/prescription-opioid-policy.pdf [cited 2015 Aug 12]
4. Dhalla IA, Persaud N, Juurlink DN. Facing up to the prescription opioid crisis. *BMJ* 2011;343:d5142.
5. Roxburgh A, Bruno R, Larance B, Burns L. Prescription of opioid analgesics and related harms in Australia. *Med J Aust* 2011;195:280-4.
6. Blanch B, Pearson SA, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia. *Br J Clin Pharmacol* 2014;78:1159-66.
7. Lembke A. Why doctors prescribe opioids to known opioid abusers. *N Engl J Med* 2012;367:1580-1.
8. Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B, et al. Trends in opioid analgesic abuse and mortality in the United States. *N Engl J Med* 2015;372:241-8.
9. Harrison CM, Charles J, Henderson J, Britt H. Opioid prescribing in Australian general practice. *Med J Aust* 2012;196:380-1.
10. Campbell G, Nielsen S, Bruno R, Lintzeris N, Cohen M, Hall W, et al. The Pain and Opioids IN Treatment study: characteristics of a cohort using opioids to manage chronic non-cancer pain. *Pain* 2015;156:231-42.
11. Ballantyne JC. What can the POINT study tell us? *Pain* 2015;156:201-2.
12. McDonough M. Safe prescribing of opioids for persistent non-cancer pain. *Aust Prescr* 2012;35:20-4.
13. Dwyer J. Coronial data on Victorian deaths involving acute drug toxicity. Presentation from the Yarra Drug and Health Forum 6 May 2013. Melbourne: Coroners Court of Victoria; 2013.
www.coronerscourt.vic.gov.au/resources/3c7fa964-bec2-4189-abb0-684f747aa6ec/cpu+-+ydhf+presentation+-+06may13+-+final+4+to+page.pdf [cited 2015 Aug 12]
14. Mendelson D, Mendelson G. Opioid regulation: time to reconsider the nomenclature and approach. *J Law Med* 2013;21:27-38.
15. Therapeutic Goods Administration. Poisons Standard 2015. Canberra: Department of Health; 2015.
www.comlaw.gov.au/Details/F2015L00128 [cited 2015 Aug 12]
16. Mendelson D. Disciplinary proceedings for inappropriate prescription of opioid medications by medical practitioners in Australia (2010-2014). *J Law Med* 2014;22:255-79.
17. Holliday S, Hayes C, Dunlop A. Opioid use in chronic non-cancer pain - part 2: prescribing issues and alternatives. *Aust Fam Physician* 2013;42:104-11.
18. eTG complete [internet]. Melbourne: Therapeutic Guidelines Limited; 2014 Nov.
19. Cohen ML. Principles of prescribing for persistent non-cancer pain. *Aust Prescr* 2013;36:113-5.
20. Health Practitioner Regulation (New South Wales) Regulation 2010. Schedule 2: Records kept by medical practitioners and medical corporations in relation to patients. Health Practitioner Regulation National Law (NSW) 2014.
www.austlii.edu.au/au/legis/nsw/consol_reg/hprswr2010580/sch2.html [cited 2015 Aug 12]
21. Good medical practice: a code of conduct for doctors in Australia. Melbourne: Medical Board of Australia; 2014.
www.medicalboard.gov.au/Codes-Guidelines-Policies/Code-of-conduct.aspx [cited 2015 Aug 12].
22. Code of Practice: Schedule 8 Substances, Volume 1 - Issuing prescriptions supplying Schedule 8 substances. Darwin: Northern Territory Government Department of Health; 2014.
www.health.nt.gov.au/library/scripts/objectifyMedia.aspx?file=pdf/18/43.pdf&siteID=1&str_title=Code%20of%20Practice%20S8s%20-%20Volume%201.pdf [cited 2015 Aug 12].

Conclusion

Due to the consistent and substantial increase in opioid prescription and associated harm to patients, the regulation of Schedule 8 drugs is of increasing relevance and importance.

The gaps in knowledge and awareness of state legislation and regulation of opioids result in medicolegal risk. Furthermore, inconsistencies across states relating to the definition of drug dependency, authorities required for prescribing, and the rules of interstate prescribing, create additional complexity for practitioners. Awareness of such intricacies is essential to reduce medicolegal risk and helps ensure the safe and effective prescription of opioids to patients. ◀

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Table Opioid prescribing in Australia: definitions of drug dependence, state and territory authority requirements* and prescription rules

State	Statutory definition of drug dependent [†]	Local authority required to prescribe opioids	Interstate prescription rules	Useful websites
		For drug-dependent patients	For non-drug-dependent patients	
ACT	A person who, due to the administration of the drug/substance, shows impaired control, or drug-seeking behaviour suggesting impaired control; and, due to the cessation of the drug/substance, is likely to experience symptoms of mental/physical distress or disorder.	Approval is required for all Schedule 8 drugs, and will only be provided if prescribing is in accordance with opioid treatment guidelines.	Approval is required if prescribing for longer than 2 months.	ACT Health: www.health.act.gov.au/ public-information/businesses/ pharmaceutical-services/ controlled-medicines
NSW	A person who has acquired an overpowering desire for the continued administration of a drug of addiction or a prohibited drug listed in Schedule 1 of <i>Drug Misuse and Trafficking Act 1985</i> (NSW).	Authority is required for all Schedule 8 drugs.	Authority is required when prescribing the following drugs for more than 2 months: - any injectable form of any Schedule 8 drug - alprazolam - buprenorphine - flunitrazepam - hydromorphone - methadone.	NSW Ministry of Health: www.health.nsw.gov.au/ pharmaceutical/doctors/Pages/ Prescribe-S8-opioid.aspx
NT	Addiction to a regulated substance means a state of physiological or psychological dependence on, or increased tolerance to, the habitual and excessive use of the substance, and includes pain and other symptomatic indications arising specifically from withdrawal of the substance.	Authority is required.	Authorisation is required when prescribing an unrestricted Schedule 8 drug for more than 15 patients. Notification is required when prescribing for more than 8 weeks or in a specific example such as the replacement of lost or stolen prescriptions. Refer to the Code of Practice Schedule 8 Substances ²² for further examples.	Northern Territory Department of Health: www.health.nt.gov.au/ Environmental_Health/Medicines_ and_Poisons_Control/Medical_Practitioners/index.aspx
Qld	A person who, as a result of repeated administration of dangerous drugs, demonstrates impaired control, or exhibits drug-seeking behaviour that suggests impaired control, over the continued use of dangerous drugs; and who, when the administration of those drugs ceases, suffers or is likely to suffer mental/physical distress or disorder.	Approval is required to prescribe Schedule 8 and Schedule 4D drugs.	Notification and treatment report are required if prescribed for longer than 2 months.	Queensland Health: www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines/drugs-of-dependence/regulation/default.asp#treatment

Table Opioid prescribing in Australia: definitions of drug dependence, state and territory authority requirements* and prescription rules (continued)

State	Statutory definition of drug dependent [†]	Local authority required to prescribe opioids		Interstate prescription rules	Useful websites
		For drug-dependent patients	For non-drug-dependent patients		
SA	A person who, due to repeated administration of prescription drugs or controlled drugs, has an overpowering desire for the administration of any such drug and is likely to suffer mental/physical distress or disorder upon cessation of administration of that drug; or has a history of consuming or using prescribed drugs in a manner that presents a risk to that person's health or which is contrary to a medical practitioner's instructions.	Authority is required to prescribe all Schedule 8 drugs.	Authority is required if prescribing for more than 2 months.	Interstate prescriptions are allowed as long as the relevant notifications and permit requirements are fulfilled.	SA Health: www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+topics/medicines+and+drugs/drugs+of+dependence
Tas.	A person who seeks to obtain a drug of dependence to sell or supply to another person, or for non-medical purposes, or as a result of administration exhibits impaired ability to manage properly the use of any such drug, or behaviour which suggests impaired ability. Failure to obtain drugs of dependence for a non-medical purpose, and consequent mental/physical distress or disorder, is also a sign.	Authority is required immediately to prescribe Schedule 8 drugs. Notification of drug-seeking or other aberrant behaviour is also required.	Authority is required to prescribe for more than 2 months. If alprazolam is concurrently prescribed, authority is required after 1 month.	Interstate prescriptions of Schedule 8 or Schedule 4 drugs cannot be dispensed in Tas.	Tasmanian Department of Health and Human Services: www.dhhs.tas.gov.au/psbtas/guidelines
Vic.	Not defined in the <i>Drugs, Poisons and Controlled Substances Act 1981</i> (Vic).	A permit is required to prescribe Schedule 8 drugs.	A permit is required to prescribe continuously for more than 8 weeks.	Interstate prescriptions are allowed as long as the relevant requirements are fulfilled.	Victorian Department of Health and Human Services: www.health.vic.gov.au/dpcs/reqhealth.htm
WA	A person who, under a state of any periodic or chronic intoxication produced by a drug of addiction or any substitute, or is under a desire/craving to take that substance/any substitute until the desire or craving is satisfied, or is under a psychic [‡] /physical dependence to take a drug of addiction or any substitute; or is listed in the register for information kept under the Drugs of Addiction Notification Regulations 1980.	Authority is required to prescribe Schedule 8 drugs.	Authority is required when prescribing for longer than 60 days (or for more than 60 days in any 12-month period).	Interstate prescriptions can be dispensed in WA if they comply with the Regulations. Further restrictions on some Schedule 8 drugs apply.	Western Australian Department of Health: www.public.health.wa.gov.au/2/1292/2/drugs_of_dependence_schedule___medicines.pm

* This does not refer to Pharmaceutical Benefits Scheme requirements.

[†] In Tasmania, the Act defines drug-seeking behaviour rather than drug dependent.

[‡] Psychic is used to legally define a drug-addicted patient in the WA Regulations.

ARTICLE

Updating the management of sexually transmitted infections

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SUMMARY

The control of sexually transmitted infections relies on case-finding and treatment of sexual contacts to prevent further transmission.

Screening for infections should be tailored to the demographic and sexual risk of the individual.

For most sexually transmitted infections, screening is performed on self-collected, non-invasive samples using highly sensitive molecular assays. These are quick and inexpensive.

Shorter courses of antivirals for genital herpes are now recommended.

New chemoprophylactic strategies for preventing HIV transmission have emerged, including treatment to prevent transmission and the use of antiretrovirals for pre-exposure prophylaxis.

Introduction

In Australia, most sexually transmitted infections are managed in primary care. The rates of infections continue to rise despite years of safe sex promotion, non-invasive screening and the availability of tests that allow self-collected samples.¹

Rates of newly acquired HIV infection have increased, and gonorrhoea notifications almost doubled between 2008 and 2012. In 2013, the highest number of syphilis cases ever was recorded. Conversely, in the same year, chlamydial infections decreased for the first time in nearly 15 years. Genital warts in young women are also declining following the introduction of the human papillomavirus (HPV) vaccination.¹

The emergence and spread of resistance to therapies among sexually transmitted bacteria and viruses now threaten our ability to effectively control infections (including HIV) in the longer term. Australian guidelines² are available for managing sexually transmitted infections, and Therapeutic Guidelines: Antibiotic has recently been updated.³

Screening

Effective management of sexually transmitted infections relies on timely, accurate diagnosis. As most infections are asymptomatic, screening is important for identifying new cases. Guidelines² and screening tools⁴ outline who should be screened (Box), what infections they should be screened for and which tests should be done. Populations vary geographically and the local epidemiology of infections may highlight other at-risk groups. Examples of these include prisoners and backpackers.^{5–7} For most asymptomatic

'check-ups', a brief discussion to ascertain sexual practices, and non-invasive or self-collected samples are appropriate and acceptable.

Screening for chlamydia and hepatitis B is recommended for all groups. Gonorrhoea screening should also be performed in young sexually active Aboriginal and Torres Strait Islander people. Gonorrhoea, HIV and syphilis screening is recommended for men who have sex with men, people who inject drugs and sex workers. People who inject drugs should also be screened for hepatitis C.⁴

Men who have sex with men

For men who have sex with men, Australian guidelines recommend serological screening for syphilis and HIV, hepatitis A and hepatitis B (in non-vaccinated individuals), and hepatitis C (people with HIV, or those with a history of injecting drug use). Updated guidelines include testing for chlamydial and gonococcal infection in the oropharynx and anorectum. Oropharyngeal and anorectal swabs should be obtained for gonorrhoea and chlamydia, and a first-catch urine sample for chlamydia.

Box Who should be offered screening for sexually transmitted infections? ⁴

Anyone requesting a screen
Sexually active people under 29 years
Men who have sex with men
Sex workers
People who inject drugs

Testing is advised up to four times a year if the man is HIV positive or there is a history of the following:

- unprotected anal sex
- more than 10 sexual partners in the preceding six months
- group sex
- recreational drug use during sex.

Any sex in the previous year should prompt at least annual screening.⁸

Testing symptomatic patients

Sexual history and physical examination play an important role for symptomatic patients, including those with complex presentations. When an infection is identified, exclude all other sexually transmitted infections by screening and treat any that are detected.

Contact tracing

Contact tracing or partner notification identifies asymptomatic cases of infection, interrupts transmission and prevents reinfection.⁸ It is an integral part of the management of sexually transmitted infections and is facilitated by ensuring confidentiality and using a non-judgemental manner. Contact tracing is a priority for HIV infection, syphilis, gonorrhoea and chlamydial infection, but is not generally useful or required for genital herpes and warts.

The time period over which to trace previous sexual contacts depends on the pathogen. The diagnosing clinician is responsible for initiating the discussion about contact tracing. Most commonly, the patient will notify their own sexual contacts (patient referral). This can be done anonymously via contact-tracing websites using texting and email messaging, or directly by telephone or face-to-face. Alternatively, with consent of the index patient, the doctor, delegate or other health agency can notify the sexual contacts (provider referral). Again, the identity of the index case may remain confidential. A mix of patient and provider referral may be appropriate with numerous contacts. Guidance for contact tracing is available online.^{9,10}

Chlamydia

Chlamydia continues to be of concern, particularly in young people – nearly 60% of all notifications are in people aged 15–24 years old. Teenage girls are three times more likely to be infected compared to their male counterparts. Most infections remain asymptomatic and untreated. This is associated with significant long-term sequelae and screening is essential for diagnosis. It is recommended in all sexually active people less than 30 years old

(<35 years old if indigenous Australian), for men who have sex with men at any age, and as part of antenatal screening depending on individual risk.

Testing for chlamydia is quick and most samples can be self-collected. Nucleic acid amplification tests (NAATs) are the preferred method. Depending on sexual behaviour, samples include first-catch urine, and blind vulvo-vaginal (preferred to urine for females), rectal and pharyngeal swabs.

Uncomplicated genital or pharyngeal chlamydia infection should be treated with a single dose of oral azithromycin 1 g. Doxycycline 100 mg twice daily for seven days is recommended for rectal infection. Contact tracing is advised, as is a test for reinfection at three months.

Gonorrhoea

While most men with urethral gonorrhoea are symptomatic, endocervical, oropharyngeal and anorectal infections are often asymptomatic. Screening for gonorrhoea is important as HIV acquisition is three times more likely in men who have sex with men with rectal gonorrhoea.¹¹ Gonorrhoea continues to be of concern in Aboriginal and Torres Strait Islander people, and travellers returning from high-prevalence countries. Sex workers providing oral sex should be screened for oropharyngeal gonorrhoea every three months.

As with chlamydia, NAATs are the preferred screening method. They can be performed on first-catch urine, and blind vulvo-vaginal (preferred in women), anorectal and oropharyngeal samples. Before treatment, request culture and sensitivity testing for men with purulent urethral discharge, and from all sample sites found to be positive for *Neisseria gonorrhoeae*.

Treatment includes a single dose of ceftriaxone 500 mg intramuscularly and azithromycin 1 g orally. Contact tracing and a test of cure are advised after treatment, particularly where first-line therapy is not administered. For the test of cure, culturing the organism is preferred over testing with NAATs. Culture testing can be conducted at one week, but testing with NAATs should be delayed until three weeks after treatment. Patients should be tested again for reinfection three months after treatment.

Growing antimicrobial resistance to treatments for *N. gonorrhoeae* has been documented in Australia and there are concerns about treating this organism in the future.

Mycoplasma genitalium infection

Although less prevalent than chlamydia in most studies, *M. genitalium* is established as a sexually transmissible cause of urethritis and cervicitis.

ARTICLE

Sexually transmitted infections

There is increasing evidence that it can cause pelvic inflammatory disease.

Genital mycoplasma polymerase chain reaction (PCR) assays allow for quick and self-collected testing and are Medicare rebatable. Suitable samples include first-catch urine in men and endocervical swabs for women. Currently, there are no recommendations to sample the rectum or oropharynx.

The current treatment is a single dose of azithromycin 1 g. However, there is increasing concern that this may induce macrolide resistance in *M. genitalium*. A test of cure should be performed four weeks after treatment is completed.

Genital herpes

It is estimated that only one-fifth of adults infected with genital herpes (type 1 or type 2) experience classical features such as recurrent blisters followed by ulceration and healing. There is a high prevalence of type 1 (seroprevalence 80%) and type 2 (seroprevalence 12%, estimates up to 25–30%) infection in Australia. Much of the management concerns counselling and health education. PCR testing of a genital swab from potential lesions is the gold standard for diagnosing genital herpes.

For recurrent herpes episodes, antiviral regimens have become shorter allowing patients more choice for managing their infection (see Table). Comparison studies have shown therapeutic equivalence for three drugs that differ only in dosing schedules and cost.^{3,12} Viral replication in recurrent infections is short-lived and standard five-day regimens offer no therapeutic advantage over shorter courses.^{12–16} The majority of patients will not require any treatment. However, when episodic therapy is unsuitable, suppressive treatment is an option (see Table).

HIV

Regular screening for populations with ongoing risk is advised. These include:

- men who have sex with men
- injecting drug users
- sexual contacts of people with HIV infection
- people diagnosed with a sexually transmitted infection, viral hepatitis or tuberculosis

- people with multiple sex partners or recent change of partner
- people reporting high-risk behaviours in high-prevalence countries
- migrants from high-prevalence countries.

Pregnant women should have HIV screening at their first antenatal visit. Testing should be done for anyone requesting it.¹⁷

Increasing HIV rates have prompted a change in the approach to treatment. Patients are now being treated earlier. This benefits the individual, and is also a public health benefit by preventing transmission.

Treatment as prevention

The efficacy of 'treatment as prevention' for HIV was shown in a multinational trial of serodiscordant couples. When the infected partner immediately commenced (rather than deferred) antiretroviral therapy and adhered to treatment, the virus was rapidly suppressed and HIV transmission was reduced by 96%. Early treatment was also associated with a 41% reduction of HIV-related clinical events.¹⁸

For prophylactic treatment to be effective, early diagnosis through expanded testing is essential. In 2012, the first rapid HIV test (Determine HIV combo) was approved. The test is a point-of-care antibody/antigen assay that can provide results in 20 minutes. It performs well in established infection, but has low sensitivity in early infection (<70%) and is inferior to routine conventional enzyme-linked immunosorbent assays performed on patient sera.¹⁹

In 2012, antiretroviral prophylaxis (pre-exposure prophylaxis or antiretrovirals for at-risk HIV-negative individuals to prevent transmission) with daily tenofovir and emtricitabine was approved for high-risk individuals in the USA. This included sexually active men who have sex with men (not in a monogamous partnership) who, in the last six months, had anal sex without a condom, a sexually transmitted infection or an HIV-positive partner.^{20,21}

Antiretroviral prophylaxis is not currently subsidised in Australia, but there are projects evaluating the implementation of this strategy. Almost all of the pre-exposure prophylaxis trials have studied daily

Table Treatment regimens for genital herpes³

Drug	5-day regimens for initial infection	Episodic treatment for recurrent infection	Suppressive treatment
Aciclovir	400 mg orally, 8-hourly for 5 days	800 mg 3 times daily for 2 days	200–400 mg orally, 12-hourly
Famciclovir	250 mg, 8-hourly for 5 days	1 g orally, 12-hourly for 1 day	250 mg orally, 12-hourly
Valaciclovir	500 mg orally, 12-hourly for 5 days	500 mg orally, 12-hourly for 3 days	500 mg daily

tenofovir alone or tenofovir and emtricitabine as a fixed-dose combination. Outcomes have been mixed. This appears to depend on adherence. In studies involving drug monitoring, if a drug was detected, efficacy ranged from 70–92%.²²⁻²⁵

Human papillomavirus

Genital human papillomavirus (HPV) infection may manifest as genital warts, premalignant lesions or squamous cell carcinomas. Pre-malignant and cancerous changes may occur in the cervix, vulva, anus and, less commonly, the vagina. HPV is more prevalent in people with HIV so cervical screening should be performed annually in these women.

The prevalence of genital warts and cervical dysplastic lesions has substantially declined in young people since the introduction of the quadrivalent HPV vaccine. It is hoped that this will translate to a decrease in cervical and other HPV-related cancer rates. Research is ongoing to determine if anoscopy screening will reduce anal cancer in HIV-infected men who have sex with men.

Syphilis

Rates of infectious syphilis increased from 5/100 000 in 2004 to 14/100 000 in 2013.¹ This was almost exclusively in men who have sex with men. Others at increased risk include indigenous Australians and people from endemic countries where infection is typically asymptomatic. These cases are usually detected by serology in the latent phase.

Presentation depends on the stage of infection. Infectious syphilis describes both primary infection, characterised by the classic chancre, and secondary syphilis which may present with a constellation of signs and symptoms such as malaise, rash, condylomata lata (wart-like lesions) and patchy alopecia. Serology remains the mainstay of diagnosis. However, in very early infection, serology can be negative. In these cases, direct detection of *Treponema pallidum* by PCR may be useful.

Hepatitis A

Rates of hepatitis A infection remain stable at below 1.3/100 000. This is punctuated by occasional outbreaks most commonly associated with travel, food-borne disease, and household and institutional contacts.¹ Sexually transmitted hepatitis A infections occur almost exclusively in men who have sex with men, and New South Wales accounts for approximately 7% of all notified cases.²⁶ Large outbreaks recorded in the early 1990s (New South Wales, Victoria and South Australia) and mid 1990s (Sydney) have prompted the recommendation of vaccination for all homosexually active men.²⁷⁻³¹

Hepatitis B

It is estimated that nearly 220 000 Australians are living with chronic hepatitis B, often acquired during childhood. Over 40% of these people remain undiagnosed.^{1,32} Rates of newly acquired infections are slowly decreasing, due in part to infant and childhood immunisation. Chronic infection mostly affects people from endemic countries. Limited data suggest that about 70% of newly acquired infections occur in Australian-born individuals.³³ Although injecting drug use is the most commonly reported exposure risk for new infection, it is estimated that sexual transmission (homosexual and heterosexual) accounts for 15–25% of cases.³³⁻³⁵

Hepatitis B is a preventable infection and vaccination should be considered for everyone, but particularly for:

- sex workers
- people who inject drugs
- men who have sex with men
- HIV-positive and other immunocompromised people
- household and sexual contacts of people with chronic hepatitis B
- Aboriginal and Torres Strait Islander people
- people with hepatitis C or other chronic liver disease
- travellers
- people from endemic countries
- prisoners
- people at occupational risk.

Hepatitis C

Some traumatic sexual practices have been implicated in sexual transmission of hepatitis C, particularly among HIV-positive men who have sex with men. In men who have sex with men, hepatitis C is more common in those who are HIV positive than those who are HIV negative (6.08/1000 vs 1.48/1000 person years).³⁶ Key risk factors include fisting, shared use of sex toys, group sex, recreational drug use during sex, current or previous sexually transmitted infections (particularly ulcerative infections) and inconsistent condom use.

The risk of transmission between heterosexuals is extremely low. Prospective studies of serodiscordant partnerships report incidence rates ranging from zero transmissions to up to 12/1000 person years.³⁷⁻⁴²

While percutaneous exposure accounts for the majority of newly acquired infections, an Australian study reported 18% of transmission due to sexual exposure. Of these, 14% were heterosexual partnerships and 86% occurred in men who have sex with men (nearly all HIV positive).⁴³

Conclusion

GPs play a key role in caring for patients with sexually transmitted infections. Effective management involves identifying and screening at-risk individuals, prescribing therapy, following up for test of cure and

test of reinfection, and initiating contact tracing with the patient. GPs can also educate patients about unsafe sex and encourage regular screening for those at ongoing risk. ◀

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REFERENCES

- 2014 Annual Surveillance Report of HIV, viral hepatitis and sexually transmissible infections in Australia. Sydney: The Kirby Institute for infection and immunity in society, University of New South Wales; 2014.
- Australasian Society for HIV Medicine. Australian STI management guidelines for use in primary care. Sydney: Australasian Sexual Health Alliance; 2015. www.sti.guidelines.org.au [cited 2015 Nov 4]
- Genital and sexually transmitted infections. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2014. www.tg.org.au/index.php?sectionid=71 [cited 2015 Nov 4]
- STI testing tool. Sydney: NSW STI Programs Unit; 2012. http://stipu.nsw.gov.au/wp-content/uploads/147045_GP_STI_Testing_Tool_2012.pdf [cited 2015 Nov 4]
- Butler T, Papanastasiou C. National prison entrants' blood borne virus and risk behaviour survey report 2004 & 2007. Perth: National Drug Research Institute & National Centre in HIV Epidemiology and Clinical Research; 2008.
- Watkins RE, Mak DB, Connelly C. Testing for sexually transmitted infections and blood borne viruses on admission to Western Australian prisons. BMC Public Health 2009;9:385.
- McNulty AM, Egan C, Wand H, Donovan B. The behaviour and sexual health of young international travellers (backpackers) in Australia. Sex Transm Infect 2010;86:247-50.
- Australian sexually transmitted infection & HIV testing guidelines 2014: for asymptomatic men who have sex with men. Sydney: STIs in Gay Men Action Group; 2014. http://stipu.nsw.gov.au/wp-content/uploads/STIGMA_Testing_Guidelines_Final_v5.pdf [cited 2015 Nov 4]
- Australasian Contact Tracing Manual. 4th ed. Sydney: Australasian Society for HIV Medicine; 2010.
- STI contact tracing tool for general practice. Sydney: NSW STI Programs Unit; 2013. <http://stipu.nsw.gov.au/wp-content/uploads/GP-Contact-Tracing-Tool.pdf> [cited 2015 Nov 4]
- Craig KJ, Meddings DR, Strathdee SA, Hogg RS, Montaner JS, O'Shaughnessy MV, et al. Rectal gonorrhoea as an independent risk factor for HIV infection in a cohort of homosexual men. Genitourin Med 1995;71:150-4.
- Abudalu M, Tyring S, Koltun W, Bodsworth N, Hamed K. Single-day, patient-initiated famciclovir therapy versus 3-day valacyclovir regimen for recurrent genital herpes: a randomized, double-blind, comparative trial. Clin Infect Dis 2008;47:651-8.
- Aoki FY, Tyring S, Diaz-Mitoma F, Gross G, Gao J, Hamed K. Single-day, patient-initiated famciclovir therapy for recurrent genital herpes: a randomized, double-blind, placebo-controlled trial. Clin Infect Dis 2006;42:8-13.
- Leone PA, Trottier S, Miller JM. Valacyclovir for episodic treatment of genital herpes: a shorter 3-day treatment course compared with 5-day treatment. Clin Infect Dis 2002;34:958-62.
- Strand A, Patel R, Wulf HC, Coates KM; International Valaciclovir HSV Study Group. Aborted genital herpes simplex virus lesions: findings from a randomised controlled trial with valaciclovir. Sex Transm Infect 2002;78:435-9.
- Wald A, Carrell D, Remington M, Kexel E, Zeh J, Corey L. Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. Clin Infect Dis 2002;34:944-8.
- Ending HIV testing table. Sydney: NSW Ministry of Health; 2014. www.health.nsw.gov.au/endinghiv/Documents/hiv-test-table-july-2014.pdf [cited 2015 Nov 4]
- Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al.; HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365:493-505.
- Conway DP, Holt M, McNulty A, Couldwell DL, Smith DE, Davies SC, et al.; Sydney Rapid HIV Test Study. Multi-centre evaluation of the Determine HIV Combo assay when used for point of care testing in a high risk clinic-based population. PLoS One 2014;9:e94062.
- Centers for Disease Control and Prevention (CDC). Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. MMWR Morb Mortal Wkly Rep 2011;60:65-8.
- US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States – 2014: a clinical practice guideline. Atlanta (GA): Centers for Disease Control and Prevention; 2014. www.cdc.gov/hiv/pdf/PrEPguidelines2014.pdf [cited 2015 Nov 4]
- Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al.; iPrEx Study Team. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010;363:2587-99.
- Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al.; Partners PrEP Study Team. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med 2012;367:399-410.
- Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al.; TDF2 Study Group. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med 2012;367:423-34.
- Chooanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al.; Bangkok Tenofvir Study Group. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofvir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2013;381:2083-90.
- Freeman E, Torvaldsen S, Tobin S, Lawrence G, MacIntyre CR. Trends and risk factors for hepatitis A in NSW, 2000-2009: the trouble with travel. N S W Public Health Bull 2012;23:153-7.
- Stewart T, Crofts N. An outbreak of hepatitis A among homosexual men in Melbourne. Med J Aust 1993;158:519-21.
- Stokes ML, Ferson MJ, Young LC. Outbreak of hepatitis A among homosexual men in Sydney. Am J Public Health 1997;87:2039-41.
- Stokes ML, Manning W. Dramatic increase in hepatitis A. N S W Public Health Bull 1998;2:77-8.
- Cameron AS, Weinstein P. Alternative hepatitis for alternative sex: recent changes in hepatitis A and hepatitis B infection patterns in South Australia. Commun Dis Intell 1991;5:244-5.
- Ferson MJ, Young LC, Stokes ML. Changing epidemiology of hepatitis A in the 1990s in Sydney, Australia. Epidemiol Infect 1998;121:631-6.
- MacLachlan JH, Allard N, Towell V, Cowie BC. The burden of chronic hepatitis B virus infection in Australia, 2011. Aust N Z J Public Health 2013;37:416-22.
- Poulos RG, Ferson MJ. Enhanced surveillance of acute hepatitis B in south-eastern Sydney. Commun Dis Intell Q Rep 2004;28:392-5.
- NNDS Annual Report Writing Group. Australian notifiable disease status, 2011: Annual report of the national notifiable disease surveillance system. Commun Dis Intell 2013;37:E313-93.
- Forssman BL, Gupta L. Enhanced surveillance of hepatitis B infection in inner-western Sydney. N S W Public Health Bull 2007;18:115-8.
- Yaphe S, Bozinoff N, Kyle R, Shivkumar S, Pai NP, Klein M. Incidence of acute hepatitis C virus infection among men who have sex with men with and without HIV infection: a systematic review. Sex Transm Infect 2012;88:558-64.
- Tahan V, Karaca C, Yildirim B, Bozbas A, Ozaras R, Demir K, et al. Sexual transmission of HCV between spouses. Am J Gastroenterol 2005;100:821-4.
- Marincovich B, Castilla J, del Romero J, García S, Hernando V, Raposo M, et al. Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples. Sex Transm Infect 2003;79:160-2.
- Kao JH, Liu CJ, Chen PJ, Chen W, Lai MY, Chen DS. Low incidence of hepatitis C virus transmission between spouses: a prospective study. J Gastroenterol Hepatol 2000;15:391-5.
- Piazza M, Sagliocca L, Tosone G, Guadagnino V, Stazi MA, Orlando R, et al. Sexual transmission of the hepatitis C virus and efficacy of prophylaxis with intramuscular immune serum globulin. A randomized controlled trial. Arch Intern Med 1997;157:1537-44.
- Vandelli C, Renzo F, Romano L, Tisminetzky S, De Palma M, Stroffolini T, et al. Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study. Am J Gastroenterol 2004;99:855-9.
- Riestra S, Fernández E, Rodríguez M, Rodrigo L. Hepatitis C virus infection in heterosexual partners of HCV carriers. J Hepatol 1995;22:509-10.
- Matthews GV, Pham ST, Hellard M, Grebely J, Zhang L, Oon A, et al.; ATAC Study Group. Patterns and characteristics of hepatitis C transmission clusters among HIV-positive and HIV-negative individuals in the Australian trial in acute hepatitis C. Clin Infect Dis 2011;52:803-11.

Depression in dementia

SUMMARY

People with dementia of any type have a high incidence of major depression.

The occurrence of a first major depressive episode in an older adult is a risk factor for developing dementia.

Management of depression in a person with dementia should be enthusiastic with an aim to optimise quality of life.

Non-pharmacological and pharmacological strategies are both important in treating depression in dementia and management of these patients requires a collaborative approach.

Selective serotonin reuptake inhibitors are the first-line pharmacotherapy for depression in dementia, although they are less likely to be effective in older people.

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Key words

Alzheimer's disease,
antidepressants, dementia,
depression

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Introduction

Depressive symptoms are quite common in older people. However, sustained and disabling major depressive episodes are more common in those with dementia than in age-matched controls without dementia. The incidence of depression may be 30% in vascular dementia and in Alzheimer's disease, and over 40% in the dementia associated with Parkinson's and Huntington's diseases.^{1,2} Practitioners caring for people with dementia should be alert to major depression as this will require specific management strategies.

The clinical picture

The symptoms and signs of major depression in dementia are often no different from depression occurring in any other group.³ Mood is most commonly low but can be irritable, angry, or anxious. Disturbed biological rhythms in sleep, appetite and energy are common and patients may be negative, hopeless or even nihilistic. Ideas of worthlessness, guilt and self-harm also occur. Overall cognitive ability may decline significantly due to the depression alone. Attributing cognitive impairment to the dementia or the depressive disorder may be difficult until an adequate trial of treatment for depression has occurred.⁴

Some signs of dementia may strongly resemble those of a major depression such as social withdrawal, lack of interest in self or others, low initiative and poor motivation. The diagnosis of the depression may be made more difficult when the dementia has not been recognised before. Apathy is a particularly confounding sign for diagnosis, and specialist assessment may be needed. Also there are some individuals whose cognitive style has always been

essentially negative and depressive, rather than this being a recent change. This may only be revealed by reliable family informants.

Typically a major depressive episode develops over weeks to a few months, and is a significant new impairment for the person. Conversely, the dementia alone may develop insidiously over months or years and be slow in progression.

The onset of the first major depression in an older adult may be the first sign of dementia that is developing or at risk of developing.⁵⁻⁷ Diagnosis of the dementia will be difficult until the depressive episode has remitted or at least improved.

Assessment

For the older person who shows a significant decline in cognition and function, the differential diagnosis must include dementia and a depressive disorder. These are not mutually exclusive. Investigations that include haematological, endocrine and other biological tests, and neuroimaging, are relevant to both diagnoses. For someone with a known dementia, of any severity, who exhibits some of the symptoms and signs of major depression, the clinician should consider and investigate for:

- new or deteriorating physical illness and the possibility of delirium
- a major depressive episode
- a phase of acute deterioration in the dementia
- the impact of prescribed and non-prescribed medicines and substances.⁸ Alcohol, marijuana, opioids and many prescribed drugs with sedative properties, can contribute to depressed mood and aggravate cognitive impairment.

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Depression in dementia

Rating scales for depression validated in the elderly population may also provide useful additional information in the assessment (see Table).⁹⁻¹³

Uncertainty of diagnosis should lead to consultation with a specialist psychogeriatrician or geriatrician.

Management of depression in dementia

An active step-wise approach to management that incorporates all potential strategies is advised in treating major depression in dementia.¹⁴

Non-pharmacological strategies

Strategies that apply to the depressed adult population can also be used for people with dementia and depression. If it is too difficult for the patient to continue with daily personal care (e.g. shopping, meal preparation, chores) during their depressive episode, relief and support should be offered. Daily activities that may raise mood, and pleasant but not onerous social and physical activity within the person's capability, should be maximised.

Positive, optimistic and 'glass half-full' thinking should be encouraged while negative thinking should be discouraged. The severity of the cognitive impairment in the depression or in the dementia may preclude useful cognitive therapy.

Although there is limited evidence for the effectiveness of specific cognitive behavioural therapies, interpersonal psychotherapy and counselling, they have been used with some benefit as part of a comprehensive management of depression and anxiety symptoms in mild dementia. These strategies require a patient to have only a mild degree of cognitive impairment for satisfactory implementation.¹⁵

Carers and family have a prominent role in supporting these strategies and may require the assistance of community nurses, social workers and occupational therapists through local community services (such as an Older Persons Mental Health Service or aged-care service).

Pharmacological strategies

Most of the original antidepressant trials did not include significant numbers of older people, or people with dementia. Clinicians often extrapolate from these trials to the dementia population, but should consider the full range of available antidepressants with caution. Antidepressants are likely to be less effective in older adults and people with dementia.^{16,17} A selective serotonin reuptake inhibitor would be a recommended first-line drug, although mirtazapine has a role when initial insomnia is a dominant symptom. Tricyclic antidepressants can cause anticholinergic effects that may further impair cognitive function in people with dementia. Other prescribing advice in this population includes:

- Titrate doses slowly while monitoring therapeutic and adverse effects, and effects on existing illnesses. The highest tolerated dose should be used. It is not appropriate to continue an ineffective low dose of an antidepressant.
- Trial an antidepressant for 4–6 weeks at the optimum dose before changing. If there is no benefit after six weeks, it should be slowly tapered and stopped.
- Review the potential for drug interactions between the antidepressant and the patient's other medicines before prescribing starts.
- Check serum sodium before starting a medication, and then after a fortnight at least, because hyponatraemia is a common adverse effect of many antidepressants. It usually develops within the first weeks of treatment.

The management of major depression in dementia requires close collaboration between the clinician and carers (including family and residential care staff). Because the dementia, plus any cognitive impairment from depression, may prevent the patient being as effective in their own care and advocacy, the burden of supervising behaviour management strategies, and the monitoring of drug efficacy and adverse effects, falls to the whole management 'team'.

Referral

The management of a possible major depression in someone with dementia should not be delayed. Specialist advice from a psychiatrist, particularly one with expertise in treating older people, should be sought in cases of diagnostic uncertainty (for either the mood disorder or the cognitive disorder), or when the depressive disorder is complicated by psychosis, persistent self-harm ideas, and failure to respond to management. Nursing and other health professionals with the local Older Persons Mental

Table Depression rating scales that have been validated in older people

Rating scale	Comment
Cornell Scale for Depression in Dementia ⁹	Has particular validity in dementia.
Geriatric Depression Scale ¹⁰	The 15-item version is useful when time is limited.
Montgomery–Asberg Depression Rating Scale ¹¹	Can be used as questionnaires and read to patients. ^{12,13} Requires training and pre-existing clinical experience in assessing depressive disorders and dementia.

Health Service may be available for advice on practical management of the depression, support to family and carers, and information on helpful local service providers.

During assessment and management, advice from a geriatrician may also be required regarding physical illness and medications, and from a clinical psychologist regarding cognitive therapy and specific behaviour and activity programs.

Some people with dementia and a major depressive episode may need hospital care to facilitate investigations, for fluid and nutritional support, and for their own safety. Electroconvulsive therapy is effective and safe in older people with dementia.^{18,19}

REFERENCES

- Enache D, Winblad B, Aarsland D. Depression in dementia: epidemiology, mechanisms, and treatment. *Curr Opin Psychiatry* 2011;24:461-72.
- Reijnders JS, Ehrh U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov Disord* 2008;23:183-9.
- Engedal K, Barca ML, Laks J, Selbaek G. Depression in Alzheimer's disease: specificity of depressive symptoms using three different clinical criteria. *Int J Geriatr Psychiatry* 2011;26:944-51.
- Rushing NC, Sachs-Ericsson N, Steffens DC. Neuropsychological indicators of preclinical Alzheimer's disease among depressed older adults. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 2014;21:99-128.
- Royall DR, Palmer R, Chiodo LK, Polk MJ. Depressive symptoms predict longitudinal change in executive control but not memory. *Int J Geriatr Psychiatry* 2012;27:89-96.
- Zahodne LB, Stern Y, Manly JJ. Depressive symptoms precede memory decline, but not vice versa, in non-demented older adults. *J Am Geriatr Soc* 2014;62:130-4.
- Boyle LL, Porsteinsson AP, Cui X, King DA, Lyness JM. Depression predicts cognitive disorders in older primary care patients. *J Clin Psychiatry* 2010;71:74-9.
- Unützer J. Clinical practice. Late-life depression. *N Engl J Med* 2007;357:2269-76.
- Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell Scale for Depression in Dementia. *Biol Psychiatry* 1988;23:271-84.
- Sheik JI, Yeasavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clin Gerontol* 1986;37:819-20.
- Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382-9.
- Kørner A, Lauritzen L, Abelskov K, Gulmann N, Marie Brodersen A, Wedervang-Jensen T, et al. The Geriatric Depression Scale and the Cornell Scale for Depression in Dementia. A validity study. *Nord J Psychiatry* 2006;60:360-4.
- Leontjevas R, van Hooren S, Mulders A. The Montgomery-Asberg Depression Rating Scale and the Cornell Scale for Depression in Dementia: a validation study with patients exhibiting early-onset dementia. *Am J Geriatr Psychiatry* 2009;17:56-64.
- Pellegrino LD, Peters ME, Lyketsos CG, Marano CM. Depression in cognitive impairment. *Curr Psychiatry Rep* 2013;15:384.
- Ortega V, Qazi A, Spector AE, Orrell M. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment. *Cochrane Database Syst Rev* 2014;22:CD009125.
- Banerjee S, Hellier J, Dewey M, Romeo R, Ballard C, Baldwin R, et al. Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. *Lancet* 2011;378:403-11.
- Nelson JC, Devanand DP. A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. *J Am Geriatr Soc* 2011;59:577-85.
- Oudman E. Is electroconvulsive therapy (ECT) effective and safe for treatment of depression in dementia? A short review. *J ECT* 2012;28:34-8.
- Hausner L, Damian M, Sartorius A, Frölich L. Efficacy and cognitive side effects of electroconvulsive therapy (ECT) in depressed elderly inpatients with coexisting mild cognitive impairment or dementia. *J Clin Psychiatry* 2011;72:91-7.

Conclusion

Depression is a serious disorder for older people with dementia. It requires early recognition, and specific assessment of contributing physical and social factors. A comprehensive treatment plan to support the patient and their carers involves the GP and community mental health and aged-care professionals. Concurrent use of non-pharmacological strategies and selected drug treatment gives the best opportunity for recovery from the depression and to reduce morbidity from the dementia. ◀

Conflict of interest: none declared



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ARTICLE

Medicinal cannabis

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Key words

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SUMMARY

A number of therapeutic uses of cannabis and its derivatives have been postulated from preclinical investigations.

Possible clinical indications include spasticity and pain in multiple sclerosis, cancer-associated nausea and vomiting, cancer pain and HIV neuropathy. However, evidence is limited, may reflect subjective rather than objective outcomes, and is not conclusive.

Controversies lie in how to produce, supply and administer cannabinoid products. Introduction of cannabinoids therapeutically should be supported by a regulatory and educational framework that minimises the risk of harm to patients and the community. The Regulator of Medicinal Cannabis Bill 2014 is under consideration in Australia to address this.

Nabiximols is the only cannabinoid on the Australian Register of Therapeutic Goods at present, although cannabidiol has been recommended for inclusion in Schedule 4.

Introduction

The intoxicating properties of cannabis have been recognised for millennia. The major psychoactive constituent of cannabis is Δ -9-tetrahydrocannabinol (THC). The non-psychoactive cannabidiol is another major component. Characterisation of these and other derivatives, as well as the receptors they interact with, has increased our understanding of the endocannabinoid system.¹

Evidence from animal studies has supported a role for cannabis derivatives and endocannabinoids in acute, visceral and cancer pain, neuro-inflammatory and neurodegenerative disorders, appetite and weight gain, cancer, seizure disorder and inflammatory bowel disease.² This has led to clinical studies of cannabis.

It is imperative that debate around medicinal cannabis use is not confused with legalisation of recreational marijuana.

Cannabis products

There is no agreed definition of medicinal cannabis. The term is used to refer to the therapeutic use of herbal cannabis and its constituents. Nabiximols is the only medicinal cannabis included on the Australian Register of Therapeutic Goods (ARTG). It is a combination of cannabidiol and THC in a spray, indicated for muscle relaxation for spasticity in multiple sclerosis. Nabiximols is a Schedule 8 drug. Cannabidiol has been recommended for inclusion in Schedule 4.³

Nabiximols is also available overseas along with other cannabis products including:⁴

- nabilone – a synthetic derivative of THC
- dronabinol – synthetic THC

- cannabidiol
- oral cannabis extract
- herbal medicinal cannabis with defined amounts of cannabidiol and THC
- unregulated cannabis.

In the Netherlands, the Office for Medicinal Cannabis oversees production of pharmaceutical grade herbal cannabis. Different strains of cannabis are cultivated under stringent conditions with strict quality control to produce herbal cannabis with variable but defined amounts of THC and cannabidiol.^{5,6} This is distributed through pharmacies and is supported by patient information.⁵

Pharmacology of THC and cannabidiol

The most studied cannabinoids are THC and cannabidiol. THC is the major psychoactive constituent of cannabis and acts as a partial agonist at CB1 and CB2 receptors.⁷ Cannabidiol is not psychoactive and is an antagonist at CB1 and CB2.⁸ It acts at multiple other receptors and can be an agonist in some systems.

Cannabidiol reduces the psychoactive effect of THC, improving its tolerability and, perhaps also, its safety by reducing the likelihood of adverse psychiatric effects. Cannabis also contains other less well characterised phytocannabinoids. Metabolites of parent compounds may also have activity.^{7,9}

The endocannabinoid system

The endocannabinoid system is complex and has numerous physiological roles including

immunomodulation, neuroplasticity, learning, emotional modulation, motivation, appetite, vascular function and gut motility.¹⁰

The cannabinoid receptors – CB1 and CB2 – are predominantly inhibitory.^{9,10} CB1 is mainly located in the central and peripheral nervous systems, altering neurotransmitter release, and CB2 on immune cells, modifying cytokine release.

Animal models of disease

A role for cannabinoid receptor modulation has been suggested in a number of diseases.^{2,7} In animal studies, CB1 receptor activation reduced nausea and vomiting, and increased feeding. It also reduced seizures and nociception in visceral pain. Reduction of intraocular pressure has also been demonstrated. Activation of the CB1 receptor may enhance survival in haemorrhagic and cardiogenic shock.

Animal studies have also shown that activation of CB1 and CB2 receptors may reduce the clinical manifestations of multiple sclerosis, neuropathic and inflammatory pain, and reduce tumour cell growth and angiogenesis in some cancers. CB2 receptor activation reduces inflammation and progression of atherosclerosis, and increases apoptosis.²

Clinical applications

Cannabis has been trialled for various indications.

Multiple sclerosis

The American Academy of Neurology has developed a consensus statement on the use of cannabinoids for multiple sclerosis. Evidence supports oral cannabis extract, THC and nabiximols for subjective, but not objective, improvements in spasticity. Oral cannabis extract reduces central pain in multiple sclerosis, while THC and nabiximols are probably effective. The efficacy of smoked cannabis in either spasticity or central pain is unclear.¹¹

HIV

A modest benefit of dronabinol has been shown in HIV-associated weight loss. However, robust data in patients receiving highly active antiretroviral therapy are not available.¹² In HIV neuropathy, smoked cannabis reduces pain, including experimentally induced pain, when assessed by changes in visual analogue scores.¹³

Chronic non-cancer pain

While cannabis and derivatives show some efficacy in pain associated with multiple sclerosis, cancer and HIV, evidence in other painful conditions is inconclusive. In patients with rheumatoid arthritis, there may be a minor effect on pain.¹³ Evidence for efficacy of cannabinoids in fibromyalgia is limited.¹³

Overall, medicinal cannabis is not recommended in chronic non-cancer pain. Indeed its psychoactive effects may cause poor engagement in multimodal, non-pharmacological pain management.¹⁴

Cancer

The US National Cancer Institute reports evidence for the use of nabiximols, nabilone and cannabis in cancer-related pain.¹⁵ Cancer Council Australia's position statement similarly acknowledges some benefit in pain, appetite stimulation and nausea.¹⁶ Nabilone and dronabinol are approved in Europe and the USA for cancer-related vomiting. There is not adequate evidence for inhaled cannabis in this indication.¹⁵

Epilepsy

There are mixed data in animal models of epilepsy. THC has been shown to be both pro- and anticonvulsant. Cannabidiol appears more promising, with some limited experience in humans.¹⁷ Preliminary data from a trial of cannabidiol (Epidiolex) found benefit in treatment-resistant paediatric epilepsy.¹⁸ This has led to much community debate, and to parents accessing cannabinoids illegally for treatment of children with catastrophic epilepsy syndromes.¹⁹

Cannabis withdrawal

Recent data show that nabiximols reduces symptoms during cannabis withdrawal, but does not impact on long-term outcomes.²⁰

Neurodegenerative disorders

The antioxidant and anti-inflammatory properties of cannabidiol have led to investigation of cannabinoids in neurodegenerative disorders including Huntington's disease, Parkinson's disease and neonatal hypoxia-ischaemia. No definitive role has been identified.⁸

Appetite suppression

Rimonabant, a CB1 receptor inverse agonist*, was available briefly for appetite suppression. However, it was withdrawn due to psychiatric adverse effects.²¹

Toxicities

The psychoactive effects of cannabis include anxiety, dysphoria, euphoria, hallucinations, paranoia, acute memory impairment and reduced cognitive performance. Acute cannabis use is also associated with increased motor vehicle accidents.²²

Increased airway diseases and oropharyngeal cancers may be risks of smoking cannabis. Other chronic toxicities include dependence, increased risk of schizophrenia and, probably, cognitive impairment.²²

* An inverse agonist binds to a receptor but has the opposite effect of an agonist.

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Medicinal cannabis

In clinical trials, discontinuations because of adverse effects were predominantly in response to psychiatric events. These were associated with higher doses of THC,¹¹ and were less common at higher doses of cannabidiol.⁵ Notably, in a number of American states where medical cannabis laws have been enacted, there is a reduction in overdose deaths from opioids.²³

Challenges

There are many challenges in considering medicinal cannabis.²⁴ Evidence supports the use of medicinal cannabis in a small number of conditions, but there is significant community pressure for use beyond these conditions.

The complexity of endocannabinoid signalling and the multiple receptor targets of cannabinoids present challenges when developing compounds with predictable efficacy and toxicity.^{8,25} Ideally, medicines are provided as refined molecules with defined pharmacology, accurate dosing, minimal adverse effects and optimal efficacy. However, it may be that therapeutic benefits are effected by the mixture of compounds in herbal cannabis, rather than by the isolated cannabinoid.

Diversion of medicinal cannabis is of concern, as is early initiation of use in adolescents. There is also the risk of accidental childhood overdose.²⁴

Canadian guidelines for cannabis 'prescribing' recognise that treatment with herbal cannabis is not a prescription per se, and suggest various methods for improving safety.^{26,27}

As in all therapeutic decisions, the principles of the quality use of medicines should be followed. These include considering if a medicine is needed and, if so, choosing one that is safe and effective in the correct formulation and dose.²⁸

In general, smoking herbal cannabis is not recommended. Vaporising or ingestion of herbal product is purportedly safer, but dosing remains inaccurate and bioavailability variable.^{4,5}

A harm-benefit assessment is critical in decision making. In terminal disease or intractable epilepsy, using products or delivery routes that might otherwise be unacceptable may be supported.

Regulation

Legislation around medicinal cannabis is complex and evolving. Products listed on the ARTG are governed by the *Therapeutic Goods Act 1989*.²⁹ The *Narcotic Drugs Act 1967* regulates narcotic cultivation and production.³⁰ The Regulator of Medicinal Cannabis Bill 2014 is currently under consideration by the Australian Government.³¹ This bill, if enacted, would provide a system for regulating cannabis independent of the Therapeutic Goods Administration, and a system for cannabis cultivation and production parallel to the Narcotic Drugs Act.³¹ Development of such a regulatory system will likely be costly.

If medicinal cannabis is to be introduced, it should be supported with prescriber and consumer education, prescriber peer review, a robust authority process and pharmacovigilance for adverse events. Hopefully we can prevent the emergence of the problems seen with prescription opioids and benzodiazepines. The regulatory framework must be responsive to changes in evidenced-based practice.

Conclusion

There is some evidence of therapeutic benefit for cannabis products in defined patient populations. While waiting for a regulatory framework, more defined products, and more definitive data to become available, a major question is whether herbal cannabis should be introduced, with appropriate legislation to prevent criminalisation, for strictly defined populations and diseases. Monitoring for individual and community safety should be a component of any model. ◀

Conflict of interest: none declared

REFERENCES

- Skaper SD, Di Marzo V. Endocannabinoids in nervous system health and disease: the big picture in a nutshell. *Philos Trans R Soc Lond B Biol Sci* 2012;367:3193-200.
- Pertwee RG. Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities. *Philos Trans R Soc Lond B Biol Sci* 2012;367:3353-63.
- Therapeutic Goods Administration. Reasons for the medicines scheduling delegates final decisions, March 2015 (Medicines). Advisory Committee on Medicines Scheduling meeting, 18 November 2014. Canberra: Australian Government Department of Health; 2015. www.tga.gov.au/book/part-final-decisions-matters-referred-expert-advisory-committee-2 [cited 2015 Nov 4]
- Mather LE, Rauwendaal ER, Moxham-Hall VL, Wodak AD. (Re)introducing medicinal cannabis. *Med J Aust* 2013;199:759-61.
- Brunt TM, van Genugten M, Höner-Snoeken K, van de Velde MJ, Niesink RJ. Therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis. *J Clin Psychopharmacol* 2014;34:344-9.
- Office for Medicinal Cannabis. The Hague: Netherlands Ministry of Health, Welfare and Sport; 2015. www.cannabisbureau.nl/English [cited 2015 Nov 4]
- Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol* 2008;153:199-215.
- Fernández-Ruiz J, Sagredo O, Pazos MR, García C, Pertwee R, Mechoulam R, et al. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? *Br J Clin Pharmacol* 2013;75:323-33.

9. Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB₁ and CB₂. *Pharmacol Rev* 2010;62:588-631.
10. Rodríguez de Fonseca F, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M. The endocannabinoid system: physiology and pharmacology. *Alcohol Alcohol* 2005;40:2-14.
11. Koppel BS, Brust JC, Fife T, Bronstein J, Youssof S, Gronseth G, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2014;82:1556-63.
12. Lütge EE, Gray A, Siegfried N. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database Syst Rev* 2013;4:CD005175.
13. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain: a systematic review of randomized trials. *Br J Clin Pharmacol* 2011;72:735-44.
14. Faculty of Pain Medicine. Statement on 'Medicinal Cannabis' with particular reference to its use in the management of patients with chronic non-cancer pain. Melbourne: Australian and New Zealand College of Anaesthetists; 2015.
15. National Cancer Institute. Cannabis and cannabinoids - for health professionals (PDQ). Bethesda (MD): National Institutes of Health; 2015. www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq [cited 2015 Nov 4]
16. Cancer Council Australia. Medical use of cannabis: a joint position statement with the Clinical Oncology Society of Australia. Sydney: Cancer Council Australia; 2014. http://wiki.cancer.org.au/policy/Position_statement_-_Medical_use_of_cannabis [cited 2015 Nov 4]
17. Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* 2014;55:791-802.
18. Devinsky O, Sullivan J, Friedman D, Thiele E, Marsh E, Laux L, et al. Abstract 3.303. Efficacy and safety of Epidiolex (cannabidiol) in children and young adults with treatment-resistant epilepsy: initial data from an expanded access program. Chicago (IL): American Epilepsy Society; 2014. www.aesnet.org/meetings_events/annual_meeting_abstracts/view/1868751 [cited 2015 Nov 4]
19. Smethurst A. Desperate parents turn to medical marijuana in last-ditch effort to improve their children's lives. Melbourne: Herald Sun [online edition]; 2014 Jan 12. www.heraldsun.com.au/news/victoria/desperate-parents-turn-to-medical-marijuana-in-lastditch-effort-to-improve-their-childrens-lives/story-fniOfit3-1226799787147 [cited 2015 Nov 4]
20. Allsop DJ, Copeland J, Lintzeris N, Dunlop AJ, Montebello M, Sadler C, et al. Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. *JAMA Psychiatry* 2014;71:281-91.
21. Public Statement on Acomplia (rimonabant): withdrawal of the marketing authorisation in the European Union. London: European Medicines Agency; 2009 Jan 30.
22. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet* 2009;374:1383-91.
23. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med* 2014;174:1668-73.
24. Bulletin series 18: The use of cannabis for medical purposes. Sydney: National Cannabis Prevention and Information Centre; 2014 Sep. <https://ncpic.org.au/professionals/publications/bulletins/the-use-of-cannabis-for-medical-purposes/> [cited 2015 Nov 4]
25. Pacher P, Kunos G. Modulating the endocannabinoid system in human health and disease--successes and failures. *FEBS J* 2013;280:1918-43.
26. Canadian Medical Protection Association. Medical marijuana: New regulations, new College guidance for Canadian doctors. Ottawa: CMPA; 2015 July. https://www.cmpa-acpm.ca/en/legal-and-regulatory-proceedings/-/asset_publisher/a9unChEc2NP9/content/medical-marijuana-new-regulations-new-college-guidance-for-canadian-doctors [cited 2015 Nov 4]
27. Kahan M, Srivastava A, Spithoff S, Bromley L. Prescribing smoked cannabis for chronic noncancer pain: preliminary recommendations. *Can Fam Physician* 2014;60:1083-90.
28. Pharmaceutical Health And Rational use of Medicines (PHARM) Committee. The National Strategy for Quality Use of Medicines. Canberra: Australian Government Department of Health; 2002.
29. Therapeutic Goods Administration. Legislation and legislative instruments. Canberra: Australian Government Department of Health; 2015. www.tga.gov.au/legislation-legislative-instruments [cited 2015 Nov 4]
30. Narcotic Drugs Act 1967, Comp. No. 9. (Jul 1, 2015).
31. Regulator of Medicinal Cannabis Bill 2014, Senate, Parl. No. 44. (Nov 27, 2014).



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FEATURE

Medicines Australia Code of Conduct: breaches

Key words

Medicines Australia, codes of conduct

Aust Prescr 2015;38:216

The Medicines Australia Code of Conduct guides the promotion of prescription products by pharmaceutical companies.¹ Each year Medicines Australia publishes a report, from its Code of Conduct Committee, which details all the complaints that have been received about advertising and other promotional activities. The Table shows the complaints where at least one breach was identified, and more details can be found in the full report.² These complaints were dealt with under the previous (17th) edition of the Code of Conduct.

This year the largest fines related to promotional events. At one event an international guest speaker gave a presentation which the majority of the Code of Conduct Committee considered was aimed to encourage discussion about the off-label use of a drug. One company was fined for organising a presentation skills course for three specialists, while

another was found not to have breached the Code for taking specialists to visit a factory in Puerto Rico.

An unusual case involved a doctor who complained about not receiving visits from company representatives, not being provided with samples and not being invited to the company's educational events. These complaints and a subsequent appeal were not upheld.

The 18th edition of the Code was implemented this year.¹ Pharmaceutical companies will now post online information about the payments (including educational support through airfares, accommodation and conference registration fees) they make to health professionals. For the first year health professionals have to consent to the disclosure, but from 1 October 2016 it will be mandatory for the industry to report any payments.

Table Breaches of the Code of Conduct July 2014 – June 2015

Company	Brand (generic) name	Material or activity	Sanction
Bayer	Nexavar (sorafenib)	Misleading detailing aid	\$10,000 fine Material withdrawn
Bayer	Xarelto (rivaroxaban)	Misleading advertising	\$30,000 fine Material withdrawn
Bristol-Myers Squibb	Sprycel (dasatinib)	Misleading promotional material	\$45,000 fine Material withdrawn
GlaxoSmithKline	Seretide (fluticasone propionate/ salmeterol xinafoate)	Fictitious patient quotes	\$40,000 fine Material withdrawn
GlaxoSmithKline	Votrient (pazopanib)	Misleading advertising	\$20,000 fine Material withdrawn
iNova Pharmaceuticals	Duromine (phentermine)	Inappropriate information at educational event	\$100,000 fine Corrective letter to participants
Novartis	Lucentis (ranibizumab)	Inappropriate educational event	\$90,000 fine
Novartis	Ultibro breezhaler (indacaterol/ glycopyrronium)	Media release	\$30,000 fine
Shire	Mezavant (mesalazine)	Unbalanced promotional material	\$20,000 fine Material withdrawn

REFERENCES

1. Medicines Australia. Code of Conduct. 18th ed. 2015. <http://medicinesaustralia.com.au/code-of-conduct/code-of-conductcurrent-edition> [cited 2015 Nov 4]
2. Medicines Australia. Code of Conduct Annual Report 2014–15. https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2014/02/20150924-FINAL-rpt-CoC-AnnualReport-2014_2015.pdf [cited 2015 Nov 4]

New drugs

Daclatasvir

Approved indication: hepatitis C

Daklinza (Bristol-Myers Squibb)

30 mg tablets

Australian Medicines Handbook section 5.5

Hepatitis C can be classified into six main genotypes (1–6). These can be further subdivided into subtypes (e.g. 1a, 1b). In Australia, genotype 1a and 1b account for 54% of hepatitis C cases and genotype 3a for 37%. Up until recently, patients were offered a combination of peginterferon and ribavirin and patients with genotype 1 disease could add a protease inhibitor. However, many people cannot tolerate interferon-based regimens or are not eligible because they have contraindications.

Several new drugs have been approved in Australia for hepatitis C.¹ Daclatasvir, a nucleotide polymerase inhibitor, adds to this list. It is a direct-acting antiviral that works by inhibiting the non-structural 5A protein involved in viral replication. Daclatasvir has been approved for use in combination with other drugs, such as sofosbuvir and asunaprevir, in patients with compensated liver disease (including cirrhosis).

The recommended dose of daclatasvir is 60 mg per day. After oral administration, daclatasvir is absorbed within 1–2 hours and steady state is reached after four days. Its terminal half-life is

12–15 hours and most of the dose is excreted in the faeces. Dose adjustment is not required in hepatic or renal impairment.

The safety and efficacy of daclatasvir in different treatment regimens have been studied in several trials (see Tables 1 and 2).

Daclatasvir and sofosbuvir

In an open-label trial of 211 patients, daclatasvir (60 mg daily) was assessed in combination with sofosbuvir (400 mg daily), with or without ribavirin.² Enrolled patients had genotype 1 (mostly subtype 1a), 2 or 3 disease with no evidence of cirrhosis. Most of them were treatment-naïve except 41 patients with genotype 1 infection who had not responded to, or had relapsed after, previous treatment with a protease inhibitor. These patients were treated for 24 weeks with the new regimen, whereas treatment-naïve patients were treated for 12 or 24 weeks. Almost all patients had a sustained response, which was defined as less than 25 IU/mL viral RNA in their serum 12 weeks after the end of treatment (see Table 1).²

Another study assessed 12 weeks of treatment with daclatasvir and sofosbuvir, but no ribavirin, in 152 patients with genotype 3 disease.³ Of the participants, 34% had been previously treated for hepatitis C, and 21% had cirrhosis. Most patients had a sustained response to this regimen, but response rates were lower in those with cirrhosis (see Table 1).

Table 1 Efficacy of daclatasvir and sofosbuvir in hepatitis C

Study	Viral genotype	Treatment regimen	Sustained virological response [‡]	
			Treatment-naïve patients	Treatment-experienced patients
Sulkowski ²	1	daclatasvir + sofosbuvir [§]	100% (70/70)	100% (21/21)
		daclatasvir + sofosbuvir + ribavirin [§]	98% (55/56)	100% (20/20)
	2 or 3	daclatasvir + sofosbuvir [§]	93% (28/30)	-
		daclatasvir + sofosbuvir + ribavirin [§]	93% (13/14)	-
Nelson ³	3	daclatasvir + sofosbuvir [#]	Overall 90% (91/101)	Overall 86% (44/51)
			Patients with cirrhosis 58% (11/19)	Patients with cirrhosis 69% (9/13)

[‡] Defined as proportion of patients with viral RNA less than the lower limit of quantification in serum, measured 12 weeks after the end of treatment.

[§] Treatment given for 12 or 24 weeks in treatment-naïve patients and for 24 weeks in treatment-experienced patients.

[#] Treatment given for 12 weeks.



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.

NEW DRUGS

Table 2 Efficacy of daclatasvir and asunaprevir in hepatitis C

Study	Viral genotype	Treatment regimen (24 weeks)	Sustained virological response [‡]		
			Treatment-naïve patients	Treatment-experienced patient	Intolerant/ ineligible patients
Manns ⁵	1b	daclatasvir + asunaprevir	90% (182/203)	82% (168/205)	82% (192/235)
Kumada ⁶			-	80% (70/87)	88% (119/135)
Jensen ⁷	1		-	Overall 93% (329/354)	-
		daclatasvir + asunaprevir +		Patients with cirrhosis 90% (66/73)	
	4	peginterferon + ribavirin	-	Overall 98% (43/44)	-
				Patients with cirrhosis 95% (19/20)	

[‡] Defined as proportion of patients with viral RNA less than the lower limit of quantification in serum measured 12 weeks after the end of treatment.

Daclatasvir combined with sofosbuvir has also been investigated in patients co-infected with HIV. Most of them had genotype 1a or 1b, and some had previously been treated for hepatitis C. After a 12-week course of daclatasvir and sofosbuvir, most of them (149/153) had a sustained virological response.⁴

Daclatasvir and asunaprevir

Daclatasvir has also been combined with asunaprevir (100 mg twice daily) in an open-label study of patients with genotype 1b infection.⁵ Asunaprevir is another direct-acting hepatitis C drug. Although approved by the Therapeutic Goods Administration, it is not currently available on prescription in Australia. It selectively inhibits the viral non-structural protein 3/4A protease.

In the trial, participants were divided into three groups:

- treatment-naïve patients
- patients who had not responded or only partially responded to previous peginterferon and ribavirin
- patients intolerant to, and/or ineligible for, peginterferon and ribavirin (this included patients with depression, anaemia or neutropenia, or compensated advanced fibrosis or cirrhosis with thrombocytopenia).

Patients with cirrhosis were present in all three groups (16%, 31% and 47%). After 24 weeks of daclatasvir and asunaprevir, most patients had a sustained virological response (see Table 2). Response rates were similar in patients with cirrhosis and without cirrhosis (84% vs 85%). A high viral titre at baseline ($\geq 800\,000$ IU/mL) or the presence of viral variants

associated with non-structural 5A protein resistance predicted a poor response to treatment.⁵

A Japanese trial also enrolled 222 patients with genotype 1b disease.⁶ They were classified as non-responders to previous interferon and ribavirin or as intolerant to, or ineligible for, interferon-based treatment. Around 10% of patients had cirrhosis. They were given 24 weeks of daclatasvir and asunaprevir. Up to 88% of participants had a sustained viral response (see Table 2), including 20 of the 22 patients with cirrhosis.⁶

Another trial investigated daclatasvir and asunaprevir with peginterferon and ribavirin in 398 patients with genotype 1 or 4 infection.⁷ Participants had been previously treated with peginterferon and ribavirin but had either not responded or had only partially responded. After 24 weeks of treatment with the new regimen, most of them had a sustained virological response (see Table 2).⁷

Safety and precautions

In the safety cohort of 1679 patients, the most common adverse events included fatigue, diarrhoea, nausea and headache. In one of the trials with daclatasvir and sofosbuvir, one patient discontinued because of fibromyalgia, and another because of a stroke. The ribavirin dose had to be reduced in five patients because of anaemia.² In a trial of daclatasvir and asunaprevir, 10 patients discontinued because of an adverse event. Reasons included increased liver enzymes (7 patients), prolonged QT interval (1), constipation (1), hypertransaminasaemia (1), brain cancer (1) and bronchiectasis (1).⁵ In the

Japanese trial of patients who were intolerant to or ineligible for interferon, 10 patients discontinued because of elevations in liver enzymes and one because of myasthenia gravis.⁶ When peginterferon and ribavirin were added to daclatasvir and asunaprevir, 18 patients discontinued. The most common reasons were rash, malaise, neutropenia and vertigo (2 cases of each).⁷

Cardiac arrhythmias, including severe bradycardia, have been reported in patients taking amiodarone with daclatasvir and sofosbuvir, so close monitoring is recommended with this combination.

Daclatasvir should not be used in pregnancy. In animal studies, it has been shown to cross the placenta, and maternal and embryofetal toxicity have been observed at high doses. Contraception should be used during treatment and for five weeks afterwards. Daclatasvir is also excreted in milk and breastfeeding is not recommended.

The safety and efficacy of daclatasvir in people who are co-infected with hepatitis B have not been established as these patients were generally excluded from the trials.

Resistance to daclatasvir can occur. If patients experience an increase in viral RNA during treatment, the regimen should be discontinued.

Drug interactions

Daclatasvir is mainly metabolised by cytochrome P450 (CYP) 3A4. It is contraindicated in combination with strong inducers of CYP3A4 (e.g. phenytoin, carbamazepine, rifampicin, dexamethasone and St John's wort), as these drugs may lower daclatasvir exposure. The daily daclatasvir dose should be increased to 90 mg with moderate CYP3A4 inducers. Conversely, the dose should be reduced to 30 mg per day with strong CYP3A4 inhibitors (e.g. clarithromycin, boceprevir, telaprevir, atazanavir, ritonavir, ketoconazole).

As daclatasvir inhibits P-glycoprotein, co-administered digoxin and other P-glycoprotein substrates with a narrow therapeutic index, such as dabigatran, should be used with caution. Care is also urged with the statins as rosuvastatin concentrations are increased with daclatasvir.

Conclusion

In general, daclatasvir-containing regimens were very effective at clearing hepatitis C virus in patients with chronic disease. This included those who had not adequately responded to previous treatments and patients who were co-infected with HIV. With the daclatasvir and sofosbuvir combination, adding ribavirin did not seem to give further benefit. Patients with genotype 3 infection who had cirrhosis were less

likely to have a sustained response after 12 weeks of daclatasvir and sofosbuvir compared to those who did not have cirrhosis. This combination was not assessed in patients with genotype 1 disease and cirrhosis. The combination of daclatasvir and asunaprevir (with or without peginterferon and ribavirin) was effective in a range of patients with genotype 1 or 4 infection.

Daclatasvir regimens were generally well tolerated but prescribers should be mindful of adverse reactions to other drugs in the treatment regimen. As daclatasvir is metabolised by CYP3A4, there are numerous drug interactions that need to be considered. Most importantly, concomitant use of strong CYP3A4 inducers is contraindicated as this may reduce the efficacy of daclatasvir.

T T manufacturer provided additional useful information

REFERENCES +

1. Thompson A, Holmes J. Treating hepatitis C – what's new. Aust Prescr 2015. Epub ahead of print.
2. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al.; A1444040 Study Group. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014;370:211-21.
3. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al.; ALLY-3 Study Team. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology 2015;61:1127-35.
4. Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A, Morgan TR, et al.; ALLY-2 Investigators. Daclatasvir plus sofosbuvir for HCV in patients coinfecting with HIV-1. N Engl J Med 2015;373:714-25.
5. Manns M, Pol S, Jacobson IM, Marcellin P, Gordon SC, Peng CY, et al.; HALLMARK-DUAL Study Team. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. Lancet 2014;384:1597-605.
6. Kumada H, Suzuki Y, Ikeda K, Toyota J, Karino Y, Chayama K, et al. Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. Hepatology 2014;59:2083-91.
7. Jensen D, Sherman KE, Hézode C, Pol S, Zeuzem S, de Ledinghen V, et al.; HALLMARK-QUAD Study Team. Daclatasvir and asunaprevir plus peginterferon alfa and ribavirin in HCV genotype 1 or 4 non-responders. J Hepatol 2015;63:30-7.

First published online 1 October 2015

Ledipasvir with sofosbuvir

Approved indication: hepatitis C

Harvoni (Gilead)

90 mg/400 mg tablets

Australian Medicines Handbook section 5.5

Sofosbuvir (Aust Prescr 2014;37:177-8) is a nucleotide analogue antiviral drug that is used in combination with other drugs to treat chronic hepatitis C. As the effectiveness of regimens containing interferon can be limited by adverse effects, there is interest in studying other drugs to use in combination with sofosbuvir.

Ledipasvir is an antiviral drug aimed at a protein (NS5A) in the hepatitis C virus. As this protein is

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involved in viral replication, ledipasvir will reduce the amount of virus in infected patients. Ledipasvir is rapidly absorbed. As the solubility of ledipasvir is pH-dependent, antacids, proton pump inhibitors and H₂-receptor antagonists can decrease absorption. Ledipasvir is minimally metabolised with most of the dose being excreted unchanged in the faeces. The median half-life is 47 hours. No dose adjustment is required in patients with hepatic impairment.

The fixed-dose combination of ledipasvir and sofosbuvir has mainly been studied in patients with genotype 1 infection. Its approval is based on open-label clinical trials which assessed the virological response (see Table). A sustained virological response was defined as a viral RNA in the patient's serum below 25 IU/mL 12 weeks after the end of treatment. However, the World Health Organization has previously considered a sustained response to be the absence of viral RNA six months after the end of treatment.

In ION-1, 865 previously untreated patients were randomised to take the combination, with or without ribavirin, in either 12- or 24-week regimens. There was a sustained viral response in 97–99% of the patients. This response was achieved by 94–100% of the patients who had cirrhosis (16% of the trial participants).¹

The ION-2 trial used the same four treatment regimens as ION-1, but studied 440 patients who had not responded to other treatments for genotype 1 infections. Approximately 20% of these patients had cirrhosis. Twelve weeks after completing 12 weeks of treatment, there was a virological response of 94–96%. In patients who were treated for 24 weeks a viral RNA below 25 IU/mL was achieved in 99%. The response rate was significantly lower in patients with cirrhosis who were treated for 12 weeks compared with 24 weeks (82–86% vs 100%).²

The ION-3 trial assessed the efficacy of a shorter treatment regimen in previously untreated patients without cirrhosis. It randomised 647 patients to take the combination of ledipasvir and sofosbuvir, with or without ribavirin, for eight weeks, or the combination alone for 12 weeks. There was a sustained virological response in 94% of the patients who took the combination for eight weeks (93% with ribavirin) compared with 95% who took it for 12 weeks.³ An eight-week regimen can therefore be considered in previously untreated patients without cirrhosis who have pre-treatment viral RNA concentrations below 6 million IU/mL.

ION-4 was an open-labelled study involving 335 patients who were infected with hepatitis C virus and HIV. Using a 12-week regimen, a sustained response against hepatitis C was achieved by 96% of the patients. Results were similar irrespective of the treatments used for HIV in the trial, and whether or not the patients had cirrhosis.⁴

Less than 1% of the patients treated with ledipasvir and sofosbuvir had to stop treatment because of adverse effects. Without ribavirin, the most frequent adverse events with the combination were fatigue, headache, nausea and insomnia. There are no human data in pregnancy and lactation, but the combination had no effect on fetal development in animal studies.

Drug interactions can occur with one or both components of the combination, so it is best to check the product information before prescribing. Its efficacy could be reduced by inducers of P-glycoprotein such as rifampicin and St John's wort. There is a potentially fatal interaction with amiodarone. Other interactions include digoxin, antiepileptic drugs, and statins particularly rosuvastatin. There is no known interaction with oral contraception.

Resistance to ledipasvir can develop during treatment. This should be considered in patients who do not have a sustained virological response.

Table Efficacy of ledipasvir and sofosbuvir in hepatitis C

Trial	Patients	Sustained virological response for patients taking 12-week regimens ‡	
		Ledipasvir/sofosbuvir	Ledipasvir/sofosbuvir plus ribavirin
ION-1 ¹	865 previously untreated patients	99% (211/214)	97% (211/217)
ION-2 ²	440 previously treated patients	94% (102/109)	96% (107/111)
ION-3 ³	647 previously untreated patients without cirrhosis	95% (206/216)	-
ION-4 ⁴	335 patients coinfecting with HIV	96% (322/335)	-

‡ Primary outcome was the proportion of patients who had no quantifiable RNA in their sera 12 weeks after treatment

A once-daily, interferon-free treatment, which in most cases only needs to be taken for 12 weeks, that has very high efficacy is an advance. While further research is needed for other genotypes, the combination of ledipasvir and sofosbuvir is probably the treatment of choice for genotype 1 hepatitis C infection in 2015. However, until similar antiviral drugs arrive, cure comes with a high cost.⁵ The Pharmaceutical Benefits Advisory Committee estimates that the cost of treatment in Australia will exceed \$3 billion over five years.⁶

T manufacturer provided the product information

REFERENCES *†

1. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al.; ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014;370:1889-98.
2. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al.; ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014;370:1483-93.
3. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al.; ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014;370:1879-88.
4. Naggie S, Cooper C, Saag M, Workowski K, Ruane P, Townner WJ, et al.; ION-4 Investigators. Ledipasvir and sofosbuvir for HCV in patients coinfecting with HIV-1. *N Engl J Med* 2015;373:705-13.
5. Hoofnagle JH, Sherker AH. Therapy for hepatitis C--the costs of success. *N Engl J Med* 2014;370:1552-3.
6. Pharmaceutical Benefits Scheme. March 2015 PBAC Meeting - positive recommendations. Canberra: Australian Government Department of Health; 2015. www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2015-03 [cited 2015 Oct 2]

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Ponatinib

Approved indication: chronic myeloid leukaemia, acute lymphoblastic leukaemia

Iclusig (Ariad Pharmaceuticals)

15 and 45 mg film-coated tablets

Australian Medicines Handbook section 14.2.3

Along with imatinib (Aust Prescr 2001;24:129), dasatinib (Aust Prescr 2007;30:50-5) and nilotinib (Aust Prescr 2008;31:49-55), ponatinib is a tyrosine kinase inhibitor for patients who have leukaemia with the Philadelphia chromosome (Ph). This chromosome results in an abnormal tyrosine kinase that causes uncontrolled growth of malignant cells. Almost all patients with chronic myeloid leukaemia and approximately 20-25% of those with acute lymphoblastic leukaemia have the chromosome.

Ponatinib is indicated for patients with chronic myeloid leukaemia who are resistant or intolerant to at least two previous tyrosine kinase inhibitors, or have the T315I mutation. Patients with this mutation are resistant to imatinib, dasatinib and nilotinib.

Ponatinib is also indicated for those with Ph-positive acute lymphoblastic leukaemia who are resistant or intolerant to dasatinib, cannot be given imatinib or have the T315I mutation.

The approval of ponatinib is primarily based on a phase II, single-arm trial. The study enrolled 449 people with chronic myeloid leukaemia (n=417) or Ph-positive acute lymphoblastic leukaemia (n=32). Almost all of the patients had experienced treatment failure with imatinib.¹

Patients were started on ponatinib 45 mg once a day. Those with chronic myeloid leukaemia were grouped into cohorts according to whether they had chronic-, accelerated- or blast-phase disease. The primary end point for those with chronic-phase disease was a major cytogenetic response (when the proportion of Ph-positive white blood cells has fallen to 35% or less) within the first 12 months. For patients with accelerated- and blast-phase chronic myeloid leukaemia or Ph-positive acute lymphoblastic leukaemia, the primary end point was a major haematological response (normal number of white blood cells or no evidence of leukaemia) in the first six months.¹

Just over half of the patients with chronic- and accelerated-phase chronic myeloid leukaemia responded to treatment. Response rates were lower in people with blast-phase chronic myeloid leukaemia and Ph-positive acute lymphoblastic leukaemia (see Table). Pre-specified subgroup analyses revealed that fewer previous treatments, younger age and shorter duration between diagnosis and treatment tended to predict a better response to ponatinib.¹

Adverse reactions were very common in the trial with 67% of patients having at least one dose interruption because of an adverse event. The most common treatment-related events (any grade) were thrombocytopenia (37% of patients), rash (34%), dry skin (32%), vascular occlusion (23%), abdominal pain (22%), neutropenia (19%) and anaemia (13%).¹ Infections occurred in over half of the people who received ponatinib - these were serious in 20% of cases and some were fatal.

Serious adverse events (grade 3 or 4) included pancreatitis (5%), abdominal pain (2%), increased lipase (2%), thrombocytopenia (2%), diarrhoea (1%), fever (1%), myocardial infarction (1%), anaemia (1%), neutropenia (1%), febrile neutropenia (1%) and pancytopenia (1%).¹ Thrombocytopenia was the most common reason for treatment interruption.

During the study, 18/449 patients died. Five deaths were thought to be related to treatment and were a result of pneumonia, fungal pneumonia, gastric haemorrhage, acute myocardial infarction and cardiac arrest. Other deaths deemed unrelated to

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Table Efficacy of once-daily ponatinib 45 mg in Ph-positive leukaemias¹

Cohort (number of patients)	Patients with a major cytogenetic response [‡]	Patients with a major haematological response [§]	Progression-free survival	Overall survival
	by 12 months	by 6 months	estimated at 12 months	
Chronic-phase CML (267 patients)	56%	-	80%	94%
Accelerated-phase CML (83 patients)	-	55%	55%	84%
Blast-phase CML (62 patients)	-	31%	19%	29%
Ph-positive acute lymphoblastic leukaemia (32 patients)	-	41%	7%	40%

CML chronic myeloid leukaemia

Ph Philadelphia chromosome

[‡] Primary outcome for chronic-phase CML (when the proportion of Ph-positive white blood cells has fallen to 35% or less)[§] Primary outcome for accelerated- and blast-phase CML and acute lymphoblastic leukaemia (when the number of white blood cells has returned to normal or there is no evidence of leukaemia)

treatment were due to sepsis (4 people), cardiac arrest (2 people), congestive cardiac failure (2 people), cardiopulmonary failure (1 person), disease progression (1 person), dehydration (1 person), hyperviscosity syndrome (1 person) and intestinal obstruction (1 person).¹

Vascular occlusion is a problem with ponatinib. Arterial and venous occlusive events occurred in 23% (101/449) of patients in the trial. These events were serious in 18% (81/449). Heart failure and left ventricular dysfunction also occurred and were serious in 5% (23/449) of patients.¹ The cardiovascular status of patients should be assessed and treated before starting ponatinib. Monitoring is recommended and treatment should be discontinued if problems develop.

As thrombocytopenia is a common adverse effect, there is an increased risk of bleeding, particularly in patients with accelerated- or blast-phase chronic myeloid leukaemia and acute lymphoblastic leukaemia. Fortnightly blood counts are recommended for the first three months then monthly after that. Serum lipase should also be regularly monitored as the majority of patients who develop pancreatitis do so in the first two months of treatment. The product information gives specific recommendations for reducing or stopping the ponatinib dose if myelosuppression or pancreatic abnormalities occur.

Increased liver enzymes and fatal liver failure have occurred with ponatinib so liver function tests before and during treatment are recommended. Caution is urged when treating patients with moderate to severe hepatic impairment.

Ponatinib is a category D drug in pregnancy. In animal studies, it was toxic and teratogenic to the

developing fetus. Breastfeeding is not recommended during treatment.

Following oral administration of ponatinib, peak plasma concentrations are reached within four hours. The terminal half-life is 22 hours and steady state is reached within a week. Most of the dose is eliminated in the faeces.

Ponatinib is extensively metabolised by cytochrome P450 (CYP) 3A4, and to a lesser extent by CYP2C8 and 2D6. CYP3A4 inhibitors (e.g. ketoconazole) may increase ponatinib exposure whereas CYP3A4 inducers (e.g. rifampicin) may lead to a decrease. Caution is urged with concomitant use of these drugs. As ponatinib inhibits P-glycoprotein, it may increase concentrations of co-administered drugs that are substrates of this transporter, such as digoxin or pravastatin. Monitoring for adverse events with these drugs is recommended.

Ponatinib may offer benefit for people with Ph-positive leukaemias who have limited treatment options. However, as there was no comparator in the trial, it is difficult to quantify the benefit. Ponatinib has serious adverse effects that often limit treatment and are sometimes fatal, so regular patient monitoring is essential. The drug comes with a black box warning about vascular occlusion and heart failure.

T **T** manufacturer provided additional useful information

REFERENCE **

1. Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre P, Paquette R, Chuah C, et al.; PACE Investigators. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med* 2013;369:1783-96.

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Tofacitinib

Approved indication: rheumatoid arthritis

Xeljanz (Pfizer)

5 mg film-coated tablets

Australian Medicines Handbook section 15.1

Rheumatoid arthritis is now managed with disease-modifying antirheumatic drugs, such as methotrexate. If there is an inadequate response, a biological drug may be prescribed. These include the tumour necrosis factor (TNF) alpha antagonists, such as adalimumab and etanercept. The choice of treatment for moderate to severe active rheumatoid arthritis has now been expanded with the approval of tofacitinib. This is a Janus kinase inhibitor, which blocks the cytokine pathway that leads to the activation of lymphocytes. The Janus kinase inhibitors therefore have effects on immune and inflammatory processes.^{1,2}

In contrast to adalimumab and etanercept, tofacitinib can be taken orally. Although a steady state is achieved after 24–48 hours of tofacitinib 5 mg twice daily, the maximum effect on lymphocytes takes 8–10 weeks. Most of the drug is metabolised, primarily by cytochrome P450 (CYP) 3A4. Tofacitinib is therefore contraindicated in severe liver disease and can interact with inducers and inhibitors of CYP3A4. As 30% of the drug is excreted unchanged, a dose reduction is recommended if the patient has a creatinine clearance below 50 mL/minute.

The clinical trials of tofacitinib assessed patients using the criteria of the American College of Rheumatology (ACR). The outcomes were measured by the reduction in the number of affected joints and improvements in other assessments. For example an ACR20 response represents a 20% change from baseline.

Tofacitinib monotherapy was studied in a trial of 611 patients who had had an inadequate response to a disease-modifying drug. Four different regimens were studied with efficacy assessed after three months. Among the patients taking the recommended dose of 5 mg twice daily, 59.8% achieved an ACR20 response compared with 26.7% of the placebo group. The corresponding results for an ACR70 response were 15.4% versus 5.8%.³

Another trial compared tofacitinib monotherapy with methotrexate in 956 patients who had not previously been treated with methotrexate. After six months 25.5% of the 369 patients who took tofacitinib 5 mg twice daily had achieved an ACR70 response. Only 12% of the 184 patients who took methotrexate achieved this response. X-rays showed significantly less disease progression with tofacitinib.⁴

Tofacitinib has also been studied in combination with methotrexate or other (non-biological) disease-modifying antirheumatic drugs. Patients who had had an inadequate response to previous treatment either added tofacitinib or a placebo. Most (79%) of the 795 patients were taking methotrexate. At six months an ACR20 response had been achieved by 52.1% of the 315 patients treated with tofacitinib and 30.8% of the 159 patients taking placebo.⁵

The combination of tofacitinib and methotrexate has been studied in a trial that investigated the radiological changes in the joints of 800 patients. After six months, 51.5% of the 321 patients who took tofacitinib 5 mg twice daily had achieved an ACR20 response compared with 25.3% of the 160 patients in the placebo groups. Compared to methotrexate alone, the combination resulted in less joint space narrowing and fewer erosions on X-ray. However, the 5 mg dose was not statistically superior to placebo at six months.⁶

For patients with arthritis that is not adequately controlled by methotrexate, adding a TNF antagonist may be considered. This strategy has been compared to adding tofacitinib in a trial involving 717 patients. There were five different regimens in this trial. Two involved starting patients on placebo before switching to tofacitinib. The comparison regimen was adalimumab injected every two weeks. At six months the ACR20 response was achieved by 51.5% of the patients taking tofacitinib 5 mg twice daily and 47.2% of the patients given adalimumab. This response was only achieved by 28.3% of the patients in the placebo groups.⁷

Tofacitinib has also been studied in patients who have had an inadequate response to TNF antagonists. The four regimens in the trial either added tofacitinib to methotrexate at the start of the study or after three months on placebo. There were 399 patients of whom 133 took tofacitinib 5 mg twice daily for six months. Most of the patients had previously tried adalimumab or etanercept. Three months after adding tofacitinib 5 mg the ACR20 response was 41.7% whereas only 24.4% of the 131 patients in the placebo groups had responded.⁸

As tofacitinib acts on the immune system, patients have a higher risk of serious infections. Hepatitis B and C, and tuberculosis should be excluded before treatment begins. Live vaccines should not be given. Serious infections in the trials included cellulitis, herpes zoster, pneumonia and urinary tract infections. Tofacitinib will reduce neutrophil and lymphocyte counts. Regular monitoring is required as neutropenia and lymphopenia may require treatment to be stopped. The patient's haemoglobin should

NEW DRUGS

also be monitored as life-threatening anaemia has been reported.⁷

Routine monitoring of liver function is recommended and the patient's lipid concentrations will also need to be measured as tofacitinib increases cholesterol concentrations. Although the relationship to tofacitinib is unclear, serious adverse events have included gastrointestinal perforation, interstitial lung disease, lymphoma and skin cancer.

Tofacitinib should not be used in pregnancy or lactation, or by women trying to conceive. It does not affect the pharmacokinetics of combined oral contraceptive pills.

While tofacitinib produces a 20% improvement in ACR criteria for some patients, there is less evidence about its effect on the long-term progression of rheumatoid arthritis. The potential advantages of tofacitinib have to be balanced against the risk of possibly fatal adverse reactions. Whether the risk of harm is greater than with other biological drugs is currently unclear. The combination of tofacitinib with other biological or immunosuppressive drugs is contraindicated. Longer term study will be needed to establish the place of tofacitinib in the treatment of rheumatoid arthritis. It will probably be reserved for specialist use in patients with arthritis that has not responded to other disease-modifying drugs.

T manufacturer provided the AusPAR and the product information

REFERENCES *A

1. Kubler P. Janus kinase inhibitors: Mechanisms of action. *Aust Prescr* 2014;37:154-7.
2. Walker J, Smith M. Janus kinase inhibitors in rheumatoid arthritis: Clinical applications. *Aust Prescr* 2014;37:158-60.
3. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al.; ORAL Solo Investigators. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* 2012;367:495-507.
4. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al.; ORAL Start Investigators. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med* 2014;370:2377-86.
5. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2013;159:253-61.
6. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al.; ORAL Scan Investigators. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum* 2013;65:559-70.
7. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, et al.; ORAL Standard Investigators. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012;367:508-19.
8. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al.; ORAL Step investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet* 2013;381:451-60.

First published online 14 October 2015

Vedolizumab

Approved indication: inflammatory bowel disease
Entyvio (Takeda)

vials containing 300 mg powder for reconstitution
Australian Medicines Handbook section 12.6

In Crohn's disease and ulcerative colitis there is an influx of inflammatory cells into the gut. Conventional treatments, such as corticosteroids, aim to reduce this inflammation. The development of biological drugs such as adalimumab and infliximab has increased the options for managing inflammatory bowel disease that has not responded to conventional treatment. Vedolizumab is a monoclonal antibody that binds to a human integrin. It reduces inflammation by inhibiting the adhesion of T lymphocytes to gastrointestinal tissues.

Vedolizumab is given by intravenous infusion. An induction regimen is followed by infusions every eight weeks. The half-life of the antibody is approximately 25 days, but how it is eliminated is uncertain. No studies have been carried out in people with renal or hepatic impairment. There have also been no studies of drug interactions.

The main trial of vedolizumab in ulcerative colitis investigated induction and maintenance therapy in patients whose previous treatments had been unsuccessful. In a double-blind part of the trial, 225 patients were randomised to vedolizumab and 149 to placebo. A second cohort included 521 patients who were given open-label vedolizumab. Induction infusions were given two weeks apart. Patients from either cohort who showed a response to vedolizumab after six weeks were randomised to receive further infusions of vedolizumab every four weeks or eight weeks, or placebo, for up to one year.

In the first cohort, after six weeks, 47.1% of the vedolizumab group and 25.5% of the placebo group had a clinical response. In the second, open-label cohort there was a response in 44.3% of patients. After a year, 41.8% (51/122) of the patients treated every eight weeks and 44.8% (56/125) of those treated every four weeks were in clinical remission. Only 15.9% (20/126) of the placebo group went into remission. Sigmoidoscopy showed mucosal healing in 19.8% of the placebo group, 51.6% of the eight-weekly group and 56% of the four-weekly vedolizumab group.¹

The main trial of vedolizumab in Crohn's disease had a similar design. It enrolled patients who had not tolerated or not responded to other drugs. One cohort compared vedolizumab and placebo while another took open-label vedolizumab for induction. Patients who responded to vedolizumab after six weeks were then randomised to continue receiving it every four or eight weeks, or to switch to placebo for up to a year.²

The response rates for the first cohort at six weeks were 25.7% (38/148) for placebo and 31.4% (69/220) for vedolizumab. In the open-label cohort 34.4% (257/747) had a clinical response. After 52 weeks of maintenance therapy 21.6% (33/153) of the placebo group were in remission. This was significantly less than the remission rate of 39% (60/154) with eight-weekly and 36.4% (56/154) with four-weekly vedolizumab.²

Another study in Crohn's disease tried to induce remission in 315 patients who had previously not responded to treatment with tumour necrosis factor (TNF) antagonists. There were also 101 patients in the trial who had not been treated with a TNF antagonist. The patients were infused with vedolizumab or placebo with repeat doses at two and six weeks. This induced remission in 13% of the placebo group and 28.7% of the vedolizumab group after 10 weeks. However, the primary efficacy end point was the remission rate in patients previously treated with TNF antagonists at six weeks. Only 15.2% of these patients achieved remission compared with 12.1% of the placebo group.

The incidence of adverse effects of vedolizumab was similar to the placebo group. Common events included nasopharyngitis, headache, arthralgia, nausea and fatigue.^{1,2} Approximately 4% of the patients developed antibodies against vedolizumab. While 4% of the patients had infusion-related reactions, so did 3% of the placebo group. As the rate of infections is increased by vedolizumab, patients should be screened for infections such as tuberculosis before treatment. No cases of progressive multifocal leukoencephalopathy were reported in the trials. Little is known about the safety of vedolizumab in pregnancy and lactation.

Assessing the effectiveness of vedolizumab after six weeks may be too soon, especially in Crohn's disease. In the main trial the response rate at six weeks was not significantly greater than placebo, although the remission rates were (14.5% vs 6.8%).² It is therefore recommended to assess the patients 12–14 weeks after starting treatment. If there is no response by then, vedolizumab should be stopped. How long treatment can safely be continued in patients who do respond is currently unknown.

As the patients who are likely to be treated with vedolizumab will have moderate to severe inflammatory bowel disease, there is a need to compare vedolizumab with other biological therapies such as adalimumab and infliximab. Only a few patients with Crohn's disease will have a sustained remission with vedolizumab if they have not previously improved with a TNF antagonist.

T **T** manufacturer provided additional useful information

REFERENCES [†]

1. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al.; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;369:699-710.
2. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al.; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;369:711-21.

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

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

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

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

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Correction

Drugs in breastfeeding

Aust Prescr 2015;38:156-9

Antineoplastics may cause bone marrow suppression – not suspension, as listed in the Table of drugs contraindicated in breastfeeding. This was an error in the print version only.

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