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Pharmaceuticals, pharmacists and profits

The Pharmacy Guild perspective

David Quilty

Executive Director National Secretariat The Pharmacy Guild of Australia Canberra

Key words

cost of drugs, generic drugs, Pharmaceutical Benefits Scheme

Aust Prescr 2014;37:146–7 First published online 4 July 2014 Community pharmacy in Australia is a public-private partnership. The delivery and dispensing of medicines is funded through the five-year Community Pharmacy Agreements between the Pharmacy Guild of Australia and the Federal Government.

The agreements also provide funding for innovative professional programs. Examples include incentives for the use of electronic-enabled prescriptions, quality care, and medication management. In addition there is funding for pharmacies to supply services for Aboriginal and Torres Strait Islander people and to support rural and regional pharmacies.¹

The Pharmacy Guild estimates Australia's community pharmacies dispense over 270 million prescriptions every year, including over 200 million² subsidised by the Pharmaceutical Benefits Scheme (PBS). These pharmacies also serve as community healthcare hubs providing support, services and advice to patients.

Like any small business, pharmacies need to achieve a reasonable return on their investments, a significant proportion of which are financed through borrowings. The infrastructure cost of the nation's 5350 privately owned pharmacies is immense and includes around \$5 billion of privately funded assets.

For 40 years, the Pharmacy Guild has been collecting data from its members to ensure it has a thorough understanding of the financial circumstances of the sector. Without adjusting for inflation, total business expenses for an average pharmacy increased by 97% in the 10 years to 2011–12, with rent and wages the main contributors. Earnings before interest, tax, depreciation and amortisation (EBITDA) averaged 6.45% of total sales in 2011–12.³ This is well below the Australian Bureau of Statistics estimates of EBITDA averages for the same year for the private health care and social assistance category (17.8%), and also fell below the average for retail trade (6.6%).⁴

Community pharmacies accept that the Australian Government must always press for the best possible deal for taxpayers from the PBS. That is why the Pharmacy Guild has consistently supported the PBS price disclosure reforms which have reaped billions of dollars in savings for the government over the past five years.

Under price disclosure, the government monitors the prices being paid by pharmacists for post-patent medicines. It then reduces PBS prices in line with the average market price. This produces significant saving to taxpayers. The forward estimates for pharmaceutical benefits and services have been reduced by over \$8 billion since the 2010–11 budget.*⁵

The budget outcome released in September 2013 found that government spending on medicines actually fell by 3.5% in 2012–13. This was confirmed in the Department of Health's annual report which revealed that PBS expenditure fell by over \$350 million in 2012–13.⁶

At 2% a year, the forecast real rate of growth in PBS expenditure is lower than the growth in gross domestic product, despite Australia's ageing population. It is significantly below the overall health system and other major drivers of health expenditure such as the Medical Benefits Schedule and public hospitals.⁷

* includes \$1.6 billion reduction in 2012–13 budget,
\$2.5 billion in 2013–14 budget, \$2 billion in August
2013 economic statement and \$2.7 billion in
December 2013 mid-year economic forecasts

From the Editor



There are several interesting new drugs in this issue. Sophisticated pharmaceuticals do not come cheap, and there will be close scrutiny of the cost to the health system. There is therefore a frequent focus on efficient use of resources. The quality use of medicines makes an important contribution, but there is always a search for other efficiencies. Zaheer-Ud-Din Babar and Agnes Vitry contrast the differences in expenditure that arise from the

differences between Australian and New Zealand funding policies. Philip Clarke also gives a health policy perspective on community pharmacy, while David Quilty explains how recent reforms affect pharmacists.

There are policies around the promotion of pharmaceuticals in Australia. Paul Biegler reveals that while regulations are aimed at what is said in advertisements, the images used can also influence our perception of a pharmaceutical product.

The Janus kinase inhibitors are an example of how increased understanding of disease processes can lead to new drug development. Paul Kubler explains how Janus kinases work, Jennifer Walker and Malcolm Smith discuss the drugs' potential in rheumatoid arthritis, and Ali Bazargan and Constantine Tam review their role in myeloproliferative neoplasms.

The distribution arrangements for the paper copies of *Australian Prescriber* have changed. As this is the first issue distributed using the new system, please contact us if you experience any problems with the delivery of your copy.

The Pharmacy Guild welcomes these trends, but it must also be recognised that, as PBS reimbursement prices fall, so does the income of pharmacies. This is because the pharmacists' fixed mark-up on medicines is directly linked to PBS reimbursement prices. Similarly, the ability of pharmacies to access trading terms (buying generic medicines for less than the PBS reimbursement price) is reduced as PBS prices fall.

The challenge is to get the right balance between ensuring the government gets maximum value from the price reductions that occur after medicines go off patent and maintaining a viable medicines sector, including a national network of community pharmacies. Until recently, this has been achieved by ensuring that each five-year Community Pharmacy Agreement takes into account the impact of PBS reforms on pharmacists' remuneration.

Pharmacies are enabling \$1 billion in savings over the life of the current Agreement. This is even after allowing for additional funding for professional programs which is provided in recognition of the impact of the expanded and accelerated price disclosure policy.

A further acceleration of price disclosure was announced by the government two days before the 2013 Federal election was called. The Pharmacy Guild believes that this tips the balance too far, threatening the future viability of pharmacies. In 2014–15, at the very time that pharmacies are most impacted by the existing price disclosure policy, a further \$30 000 will be stripped off their financial bottom lines. This means that, for the average pharmacy, the total reduction in dispensary related gross profits will be \$90 000 next financial year.

A number of think tanks and academics assert that Australia still pays too much for off-patent medicines and that reform of the PBS should go further.

For example, the Grattan Institute has released a report concluding that if Australia benchmarked its medicine prices against New Zealand and the United Kingdom, taxpayers could save more than \$1 billion.⁸ It is important that such reports recognise that the different medicines systems overseas have real impacts on patient choice and the ready availability of medicines.

The Grattan Institute acknowledges the negative flow-on effect of reduced medicine prices on community pharmacies, stating that 'better prices would significantly reduce income for community pharmacies'. As a solution it advocates 'expanding the services that pharmacies can provide, giving them new sources of income' and raises the option of 'direct, transparent subsidies to community pharmacies in locations where viability may be an issue'.⁸

The Guild strongly supports an enhanced role for pharmacists and is putting significant work into developing new primary healthcare models for community pharmacies. However, these new models are only feasible if pharmacies continue to be properly remunerated for their core role of dispensing medicines safely and responsibly to patients. ◄

Conflict of interest: none declared

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Pharmaceuticals, pharmacists and profits

A health policy perspective

Philip Clarke

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Key words

cost of drugs, generic drugs, Pharmaceutical Benefits Scheme

Aust Prescr 2014;37:148-9 First published online 4 July 2014 In the past, the Australian Government paid lower prices than other countries for new drugs. However, after patent expiry there was no effective mechanism to adjust the amount paid. The introduction of generic drugs only produced modest price reductions.^{1,2} Consequently, the Australian Government and some consumers were paying very high prices for generic drugs when compared to other countries such as England. Australian pharmacists benefited from these high prices as the pharmaceutical industry was supplying them with these products at a discount. The wholesale price was well below the amounts the pharmacists were paid for supplying these drugs through the Pharmaceutical Benefits Scheme (PBS).³

Reforms to the pricing of pharmaceuticals were introduced in 2007. One of the key elements of these reforms was price disclosure. This based future payments to pharmacists on the actual wholesale prices they paid for generic drugs. The Health Minister at the time said this provided a way of 'harvesting for the benefits of taxpayers these discounts, which have historically been going to pharmacists'.⁴ Pharmacists were paid compensation for these reforms, but this was intended to be for a limited period of time. The Minister went on to say:

The reason why the savings to government become much more significant in five years time and beyond is because there are about 100 major drugs that are coming off patent in that time and we are compensating pharmacists, we are explicitly compensating pharmacists for the loss of discounts over the next four years, but we are not explicitly compensating them for the much greater impact of the loss of discounts in the subsequent five and more years.⁴

A problem with the original policy of price disclosure was that it was largely voluntary to supply the information on actual wholesale prices. As a result, in the first round of price reductions in 2009, only four generic drugs fell in price. Commenting at the time, the Pharmacy Guild claimed that this debunked 'myths about the extent to which community pharmacies are given discounts on generic drugs'.⁵ Under the original price disclosure policy it took 18 months, from when the purchase prices were first disclosed, before the reimbursements to pharmacists were reduced to reflect these lower prices. Community pharmacy in Australia is now going through a period of change brought about by the expiry of the patents on an increasing number of commonly used drugs. As generic versions of these drugs should be cheaper this should mean much lower prices for taxpayers and consumers, and will free up resources for allocation to other parts of the healthcare system. For pharmacies this poses challenges as their profit margins will fall if the PBS price is closer to the discounted wholesale price.

The Pharmacy Guild has recently campaigned for compensation after further changes were introduced in August 2013.⁶ These aim to make additional savings by speeding up price disclosure and the rate at which prices of generics fall. However, if the government compensates pharmacists for more rapidly declining generic prices, should it not also compensate firms that sell computers or mobile phones, as they also face declining profit margins from falling prices? Do Australian pharmacists have a special entitlement to taxpayer funds to ensure their profitability without having to adapt to changing circumstances?

Looking ahead we can learn from the experience of other countries such as England, which has much lower generic prices. Importantly, England uses a price disclosure system, but adjusts prices downward every three months, which is four times faster than in Australia. It also uses a system of 'clawbacks' to regulate the profits that can be made by independent pharmacies through discounts.⁷ While these changes may have impacted on some pharmacists' profit margins, the number of pharmacies operating in England has risen by 15% since 2005.8 This shows that it has not had a negative impact on the overall viability of pharmacy. While pharmacy in England also faces challenges, the Royal Pharmaceutical Society is focusing on developing new models of practice, rather than seeking compensation for the impact of past reforms.8

We must also evaluate the benefits and costs of policies designed to maintain the system of community pharmacy in Australia which includes restrictions on pharmacy ownership and geographic location. In the 21st century, when consumers are increasingly purchasing a wide range of goods through the internet, is it the role of the government to regulate where new pharmacies should be physically located? Does the Australian consumer really benefit from ownership restrictions that date back to the 1930s, when legislative change was introduced to prevent the British pharmacy chain 'Boots' from entering the Australian marketplace?⁹

Unfortunately, there is very little independent evidence to examine these questions. Last year the McKeon Review¹⁰ into health and medical research in Australia suggested that the government invest 3–4% of current health expenditure on research to improve the healthcare system. The most recent Guild-Government Community Pharmacy Agreement involved \$15.4 billion worth of funding for 5000 community pharmacies in Australia.¹¹ While there is currently a review of the administration of the agreement by the Australian National Audit Office, there is a need to examine broader questions regarding the regulation of community pharmacy. A transparent review of the community pharmacy sector conducted by the Australian Productivity Commission could look at the impact of current policies and evaluate options for reform. Such a review could identify the scope for efficiencies, while taking into account the special needs of some consumers (such as those living in rural areas). Surely it is time for some evidence-based policy, rather than 'behind closed door' negotiations, to shape the role and contribution of pharmacy to the Australian healthcare system. <

Conflict of interest: none declared

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Editor's award

Dr John Dowden, the Editor of *Australian Prescriber*, was recently awarded a Fellowship of the Royal College of Physicians of Edinburgh for his contribution to drug education in Australia and internationally. He is seen here receiving his award from Professor Derek Bell, the President of the College, at the official ceremony in Edinburgh in June this year.



http://5cpa.com.au/about-5cpa [cited 2014 Jun 20]

Differences in Australian and New Zealand medicines funding policies

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Key words

cost of drugs, Pharmaceutical Benefits Scheme

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In 2011 Australia spent US\$587 on pharmaceuticals per capita, while New Zealand spent US\$288

Australia and New Zealand are well known internationally for having implemented national medicines policies that aim for equitable access to cost-effective and safe medicines. However, each country adopted a different approach.

In 2011, Australia spent more than double what New Zealand spent on pharmaceuticals per capita. Australia spent US\$587 (around 22% more than the Organisation for Economic Co-operation and Development (OECD) average) while New Zealand spent US\$288 (around 40% less than the OECD average).¹ A 2011-12 analysis of the 73 individual drug-dose combinations that are prescribed the most often or account for the most expenditure in Australia showed that Australian prices were, on average, eight times higher than New Zealand's. If Australia adopted New Zealand's prices for 62 identical drug-dose combinations, which are available in both countries, the total Pharmaceutical Benefits Scheme (PBS) expenditure would be reduced by A\$1.1 billion a year.²

New Zealand is able to achieve savings because of a combination of program budgeting, tough price negotiations and different procurement mechanisms, such as competitive tendering.³ Some of these policies have been emulated with success in other countries. However, the New Zealand policies are criticised because fewer medicines, including new drugs, are subsidised compared to other countries. A comparative analysis of the approval and funding

> of new drugs showed that only 59 (43%) of the 136 medicines listed in the Australian PBS between 2000 and 2009 were listed in the New Zealand Pharmaceutical Schedule. The listings in New Zealand occurred, on average, 32.7 months after Australia.⁴ In another study comparing the funding of cancer drugs in 13 countries or regions, New Zealand was the country that reimbursed the fewest indications.⁵ These differences are partly due to the Pharmaceutical Management Agency

of New Zealand (PHARMAC) operating on a capped budget. It therefore prioritises new drugs against each other and against access to all medicines. In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) also considers the cost-effectiveness of new drugs compared with current standard of care, but has no capped budget. The decision to subsidise an item has to be determined by the Minister for Health if the net cost to the PBS is greater than \$20 million per year.

Australia has introduced new pricing policies that involve price disclosure by manufacturers to the government, including incentives and discounts to pharmacies. Australian consumers support accelerating these price cuts, but there are concerns that they will affect the profitability of pharmacies.^{6,7}

Only a minority of new drugs provide a definite therapeutic advantage over standard treatments. Of the 217 approvals by the Australian Therapeutic Goods Administration between 2005 and 2007, only seven were rated as important therapeutic innovations.⁸ Most of the drugs funded in Australia and not in New Zealand were additions to an existing therapeutic class rather than new drugs providing important therapeutic benefits.⁴ New Zealand is less likely to fund 'me too' products.

There is a dearth of research on whether or not the lack of access to some innovative medicines in New Zealand, or switching patients to different brands of medicines, adversely affects patient outcomes. On the other hand, New Zealanders may have access to some forms of treatment that are not funded in Australia. For example, insulin pumps are subsidised for all patients with type 1 diabetes in New Zealand, but only in children and adolescents under 18 years in Australia. There are benefits if unnecessary new drugs are not funded and the savings are allocated to more effective interventions. New Zealand has chosen to keep lower co-payments for prescriptions (NZ\$5 or less per script for most people) than in Australia (A\$36.90 for general patients or A\$6 for people with concession cards). The higher co-payments in Australia raise an important equity issue. A study showed that the 21% increase in the co-payments in 2005 adversely affected prescription medicine use.9

The population is ageing so the use of medicines will increase. Policy challenges ahead include growth in medicines expenditure, and consumer expectations that expensive specialised medicines will be funded by the government. In both countries, concerns have been expressed that the Trans-Pacific Partnership Agreement may affect access to affordable medicines by delaying the availability of generic medicines and by changing the funding policies.^{10,11} There is currently a move to harmonise the regulation of medicines in Australia and New Zealand with the creation of an Australia New Zealand Therapeutic Products Agency, but there are no current plans for harmonising funding models.

Until now there has been limited public debate on what the priorities are for Australia and New Zealand, including which decision criteria should be used to fund new drugs and at what price. In Australia, the PBAC publishes all its decisions as public documents, but the judgements embedded or implicit in these decisions are not widely debated. Although there is general satisfaction with access to medicines in Australia, there are concerns about delayed funding of new drugs. Industry-supported groups such as the Oncology Industry Taskforce and the Cancer Drugs Alliance argue that the listing of new cancer drugs on the PBS is worryingly low and call for reforms of the current funding processes. However, Australia pays more than other countries for drugs such as statins which, if they had been bought more cheaply, could have freed funds for new drugs.

In New Zealand there are concerns about access to high cost drugs, red tape in accessing unlisted

treatments for individual patients, and equitable access for Maori and Pacific Island people.¹⁰ Many submissions to a public consultation by PHARMAC reported negative experiences in relation to the lack of access to some drugs and that the financial impact of decisions outweighed the consideration of other criteria.12 In response to this consultation, PHARMAC has announced that it will develop a proposal for change. Public input and consumer engagement in debates around medicines policies and priorities are essential for ensuring the continuous commitment of health authorities to community values and maintaining public confidence in government decision-making processes. It is important that this debate is not driven by the pharmaceutical industry, which is mostly motivated by ensuring high profits for its new drugs whatever their effectiveness. Australian and New Zealand citizens need to be independently informed about the delicate balance between equity and costeffectiveness, and between individual and societal needs when funding new drugs. We need an open informed public debate on the choices that have to be made to ensure equitable and sustainable access to new drugs in the future. ◀

Conflict of interest: none declared

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Letters to the Editor

Intravenous paracetamol in paediatrics: cause for concern

Editor, – I disagree with the statement in the medicinal mishap (Aust Prescr 2014;37:24-5) that only one route of administration for paracetamol should be charted when treating children.

It is neither inappropriate nor unsafe. It reduces the flexibility of the nurses to decide whether the intravenous or oral route is used. The child may initially require intravenous then oral dosing (much cheaper) when suitable. The doses and dosing intervals are the same for the oral and the intravenous formulations. Rectal doses are higher, but it would not be unsafe to prescribe paracetamol 'IV/PO/PR'. Certainly 'IV/O' is perfectly acceptable. It is not practical to prescribe per rectum paracetamol in doses that are not in multiples of 125 mg.

Secondly, there is not enough room on the current standardised medication chart (which needs to be revised) to include the generic and the brand name (which is often not known to the prescribing doctor).

Greg Lumsden Anaesthetist Perth

Editor, – The medicinal mishap makes the statement that writing up paracetamol IV/PO/PR is unsafe. Compared to what, may I ask? Compared to writing it up on three separate sections of the chart? Writing it up on one section, I feel, makes it less likely that multiple doses are given and the daily maximum is exceeded. Postoperatively, I know that initially my patients will require intravenous administration and will progress to oral when their gut function recovers.

Peter McLaren Anaesthetist Southport Qld

Madlen Gazarian, Anna Drew and Alexandra Bennett, the authors of the medicinal mishap, comment:

We thank Dr Lumsden and Dr McLaren for their correspondence and appreciate the opportunity to provide important clarifications about NSW Therapeutic Advisory Group's (TAG) guidance on intravenous paracetamol.¹² First, a fundamental principle of good therapeutics is to prescribe medicines by specifying only one route. Reasons include different indications and doses appropriate for the same medicine administered by different routes. This principle is highlighted well by paracetamol but also applies to other medicines such as morphine.

Our article recommended that intravenous paracetamol be reserved for 'short-term treatment of mild-moderate pain when enteral administration is not possible'. In addition, we recommended that treatment is reviewed daily and the intravenous prescription discontinued as soon as it is no longer needed. This is also an important risk-management strategy which eliminates exposure to potential ongoing risk (for example, 10-fold overdoses) when there is no additional efficacy benefit from intravenous over enteral administration.

Second, a general principle for safe paediatric prescribing is that prescribers 'check the basis for the dose calculation in a current paediatric prescribing reference or other up-to-date, evidence-based medicines information resource'. Current national³ and international⁴ paediatric dosing references and NSW TAG's own guidance^{1,2} recommend different individual doses, dose intervals and maximum safe daily doses for intravenous, oral and rectal paracetamol for different indications. For these reasons we re-emphasise that 'prescribing paracetamol IV/PO/PR is inappropriate and unsafe'.

While acknowledging the national inpatient medication chart could be improved, our recommendation to 'specify the brand name in addition...' could be accommodated by the current paediatric chart by writing the brand name in the 'Pharmacy/Additional information' section.

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

Glycated haemoglobin

Editor, – In response to the informative article by Michael d'Emden on glycated haemoglobin for the diagnosis of diabetes (Aust Prescr 2014;37:98-100), I wish to comment on the discrepancies between blood glucose and HbA1c tests. While it is noted that blood glucose is minimally elevated in patients with an HbA1c of less than 6.5%, often the first derangement noted in general practice is a fasting blood glucose concentration in the diabetic range. Patients may have had this level for years before the HbA1c climbs over 6.5%.

There is increasing evidence of clinical benefit from early medical intervention in type 2 diabetes.¹ I am therefore concerned that by relying on the HbA1c as a single diagnostic test there is a missed opportunity to prevent disease progression using early dietary and lifestyle education and/or metformin in patients with impaired fasting glycaemia as a result of worsening insulin resistance.

Ashraf Saleh GP Toowoomba Qld

REFERENCE

 Garvey WT, Ryan DH, Henry R, Bohannon NJ, Toplak H, Schwiers M, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extendedrelease. Diabetes Care 2014;37:912-21.

Michael D'Emden, the author of the article, comments:

The article did not state that the HbAlc should be the only test used for diagnosis of type 2 diabetes. In the concluding paragraph, it says 'the acceptance of HbAlc testing will provide an additional tool to assist in the early diagnosis of diabetes. But it should not be the only tool.'

HbA1c is one of several biochemical tests that can be used to establish the diagnosis. They each have an important role in different clinical circumstances. The Australian Diabetes Society's HbA1c committee clearly acknowledges the important role of blood glucose measurements for the diagnosis of diabetes, in its position statement.¹

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 d'Emden MC, Shaw JE, Colman PG, Colagiuri S, Twigg SM, Jones GR, et al. The role of HbA1c in the diagnosis of diabetes mellitus in Australia. Med J Aust 2012;197:220-1.

The 'polypill'

Editor, – It is interesting to see the 'polypill' surface again (Aust Prescr 2014;37:82-6). In 2004, the BMJ published a study that showed the 'polymeal', a combined meal of seven food components, could limit cardiovascular mortality by 75% and was at least equivalent in effect to the polypill. The study's conclusion was 'Finding happiness in a frugal, active lifestyle can spare us a future of pills and hypochondria'.

John Marley

Professor Faculty of Medicine and Biomedical Science University of Queensland

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Professor Marley enjoys all foods present in the polymeal and refuses to take pills



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Janus kinase inhibitors

Mechanisms of action

SUMMARY

The Janus kinase family of enzymes are associated with cytokine receptors on the surface of cells. They are part of the Signal Transducer and Activation of Transcription pathway which is involved in inflammatory and immune responses.

An abnormality in the pathway can cause abnormal proliferation of cells. Possible outcomes include polycythaemia vera, leukaemia and lymphoma.

Inhibiting Janus kinase can reduce immune responses. This can lead to improvements in autoimmune conditions such as rheumatoid arthritis.

Ruxolitinib and baracitinib mainly inhibit Janus kinase 1 and 2. Tofacitinib inhibits Janus kinase 1 and 3.

As Janus kinase inhibitors alter the immune response they increase the risk of serious infections. There is a possibility that they may also increase the risk of cancer.

Introduction

Many diseases related to the immune system involve abnormal production of cytokines, a group of proteins which enable cells to signal each other. For example, the cytokine interleukin-2 stimulates the production of T cells. After a cytokine binds to its receptor, an enzyme called Janus kinase (JAK) contributes to the processes within the cell to produce an immune or inflammatory response. Inhibiting this enzyme may be beneficial in some haematological malignancies and autoimmune diseases including rheumatoid arthritis.

Janus kinase takes its name from the Roman god Janus. As Janus had two faces he could look in two directions and so statues of Janus were often placed at gateways or doors. Janus kinase has two domains and is located at the entry to cells.

Janus kinase-Signal Transducer and Activation of Transcription signalling

Cytokines such as interferons, interleukins and colony stimulating factors play a critical role in cell proliferation and differentiation, metabolism, haematopoiesis, host defence, apoptosis and immunoregulation.¹ Cytokines function by binding to specific receptors on cell membranes. There are two large subgroups of cytokine-receptor interactions that cause signal transduction via the Janus kinase-Signal Transducer and Activation of Transcription (JAK-STAT) pathway.² This pathway is a crucial intracellular conduit by which many cytokines interact with their receptors (see Fig.):

- type I receptors bind several interleukins, colony stimulating factors and hormones such as erythropoietin, prolactin and growth hormone
- type II receptors bind interferons and interleukin-10 related cytokines.³

Janus kinases

The Janus kinases are part of the tyrosine kinase group of enzymes (Table 1). At present, four important members of the Janus kinase family have been identified. They all selectively interact with the intracellular parts of the receptors. Janus kinase 1 and Janus kinase 2 are involved in a broad range of functions including host defence, haematopoiesis, neural development and growth. In contrast, Janus kinase 3 and tyrosine kinase 2 have a narrower role in the immune response.² Janus kinase 3 is predominantly expressed in haematopoietic cells and is critical for signal transduction of interleukins integral to lymphocyte activation, function and proliferation.

As well as the functional part of the Janus kinase molecule, there is a similar part which is thought to be inactive. This 'second face' is known as the pseudokinase domain.

Signal Transducer and Activation of Transcription

The family of transcription factors includes Signal Transducer and Activation of Transcription (STAT) 1–5a, 5b and 6. Activation of the Janus kinases leads to phosphorylation of receptor chains and formation

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of docking sites for the STATs.⁴ After phosphorylation the STATs translocate to the nucleus where they bind to DNA and regulate gene expression.¹ They can both activate and repress gene transcription (Fig.).⁴

Janus kinase abnormalities

Animal models have shown that the JAK-STAT pathways and the cytokines using these pathways play a critical role in the pathogenesis of autoimmunity, allergy, asthma and haematopoietic disorders. Any mutations which cause a gain or loss of function of JAK-STAT, and variations in the genes encoding cytokines and their receptors, are associated with a significant increase in immune-mediated disorders (Table 1).

V617F is an activating mutation in the pseudokinase domain of Janus kinase 2. Activating this normally inactive domain produces kinase activity which can lead to proliferation of haematopoietic cells.^{5,6} This causes polycythaemia vera and other myeloproliferative processes.

Alteration of the receptors associated with Janus kinases can contribute to diseases such as leukaemia and myelofibrosis. For example, loss-of-function mutations in the interleukin-2 receptor–Janus kinase 3 signalling pathway are responsible for some cases of severe combined immunodeficiency syndrome.

Sometimes cells abnormally secrete cytokines. This can lead to persistent activation of Janus kinases. Examples of this autocrine cytokine secretion include secretion of interleukin-13 in primary B cell lymphoma and Hodgkin lymphoma. Interleukins-6 and -10 activate Janus kinases in activated B cell-like lymphomas. This secretion leads to increased survival of malignant cells.

Sometimes Janus kinases can be involved in changing the activity of a gene without binding to DNA. For example, the Janus kinase 2 V617F mutation that is associated with myelofibrosis can directly phosphorylate chromatin targets in the nucleus. This exerts an effect on gene transcription that is independent of STATs.

Janus kinase inhibition

Inhibiting Janus kinase interrupts the JAK-STAT pathway. One effect of this inhibition in myelofibrosis is a significant reduction in splenomegaly with overall improvement in associated symptoms.⁴

Janus kinase inhibition has been widely studied in rheumatoid arthritis as there is overproduction of interleukin-6, interleukin-12, interleukin-15, interleukin-23, granulocyte-macrophage colony stimulating factor and interferons.⁷ The cytokine

Fig. Signalling through the JAK-STAT pathway



receptors are therefore very prominent in driving autoimmunity particularly through Janus kinase 1 and 3. Inhibition of Janus kinase 1 and 3 will inhibit signalling and therefore suppress immune responses.

Due to the critical role of Janus kinases in host defence, autoimmunity and haematological cancers, they have become an attractive target for therapeutics for a variety of disorders (Table 2).

Ruxolitinib

Ruxolitinib is a Janus kinase 1 and 2 inhibitor that selectively targets myeloproliferative disorders involving the gain of function mutation in Janus kinase 2 (V617F mutation). It reduces splenomegaly and systemic symptoms, and improves overall survival in myelofibrosis. It is also being studied in rheumatoid arthritis and skin psoriasis.⁸

Ruxolitinib is largely eliminated by hepatic cytochrome P450 3A4 metabolism, warranting care when choosing

Janus kinases Associated cytokines		Associated diseases		
	Loss of function mutations	Gain of function mutations		
Janus kinase 1	interleukin-2, 4, 6, 7, 9, 10, 11, 13, 15, 19, 20, 21, 22, 24, 26, 29	-	T and B cell acute lymphoblastic leukaemia	
	oncostatin M		acute myeloid leukaemia	
	leukaemia inhibitory factor	\langle	acute myeloid leukaemia with severe	
	granulocyte colony		congenital neutropenia	
	granulocyte colony stimulating factor		activated B cell-like diffuse large B	
	tumour necrosis factor	Ĺ	lymphoma	

Janus kinase inhibitors - Mechanisms of action

erythropoietin

prolactin

leptin

growth hormone

thrombopoietin

granulocyte colony stimulating factor

tumour necrosis factor interleukin-3, 5, 6, 13 interferon gamma

interleukin-2, 4, 7, 9, 15, 21

interleukin-10, 12, 22, 26, 29

interferon alfa/beta/omega interleukin-28 alfa/beta

leukaemia inhibitory factor

oncostatin M

neir mutations

severe combined

immunodeficiency

primary immunodeficiency

other drugs for patients. Starting doses are generally lower for patients with renal impairment.

Baracitinib

Janus kinase 3

Tyrosine kinase 2

Janus kinase 2

Baracitinib is also an inhibitor of Janus kinase 1 and 2. It has shown clinical efficacy in patients with severely active rheumatoid arthritis resistant to other treatments.

Tofacitinib

Tofacitinib is principally an inhibitor of Janus kinase 1 and 3. It also inhibits Janus kinase 2 to some extent, but has very little effect on tyrosine kinase 2. There is some evidence that it may have an effect in patients with rheumatoid arthritis that has not responded to other therapies.

Adverse effects of Janus kinase inhibition

As Janus kinase inhibitors alter the immune response, there is an increased risk of serious bacterial, fungal, mycobacterial and viral infections including opportunistic infections like tuberculosis and

non-disseminated herpes zoster. This can be attributed to a reduction of natural killer cells as a consequence of Janus kinase 1 and Janus kinase 3 inhibition.³ There is also a potentially increased risk of cancer as a result of blocking the action of interferons and natural killer cells, as these play an important role in tumour surveillance. Unresolved concerns about safety led the European Medicines Agency to conclude that the benefits of tofacitinib did not outweigh the potential harms.9

polycythaemia vera

Hodgkin lymphoma

myelofibrosis

essential thrombocytosis

Down syndrome-associated B cell acute lymphoblastic leukaemia

megakaryoblastic leukaemias

primary mediastinal B cell lymphoma

Erythropoietin and colony stimulating factor activate Janus kinase 2. Anaemia, neutropenia and thrombocytopenia may therefore be consequences of Janus kinase 2 inhibition.

Future developments

As Janus kinase inhibitors block cytokines they are being studied in diseases such as psoriasis, inflammatory bowel disease, transplantation and systemic lupus erythematosus. There is a potential role for an inhibitor of Janus kinase 1 and 2 like tofacitinib in asthma and

allergy as these conditions are associated with T-helper lymphocytes and the action of interleukin-4, which will require Janus kinase 1 and 2 for signalling.

Ruxolitinib and tofacitinib are non-specific JAK inhibitors as they act on more than one kinase. There are several trials investigating whether selective Janus kinase inhibitors have better safety with comparable efficacy. <

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Drug	Janus kinase inhibition		
	Janus kinase		
	1	2	3
ruxolitinib *	\checkmark	\checkmark	-
baricitinib	\checkmark	\checkmark	-
tofacitinib	\checkmark	\checkmark	\checkmark
pacritinib	-	\checkmark	-
momelotinib	\checkmark	\checkmark	-

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Undergraduate student prize 2014

Congratulations to Veronica Ho, the winner of the 2014 pre-registration student prize, sponsored by *Australian Prescriber*, and awarded by the Australian and New Zealand Association for Health Professional Educators (ANZAHPE).

Veronica is a third-year student in the Bachelor of Medicine, Bachelor of Surgery program at the University of New South Wales. Her project was 'Online testable concept maps for learning about pathogenesis of disease'. She developed an online learning tool where students could test their knowledge of the pathogenesis of a disease by dragging and dropping missing pieces of information into a visual representation of the disease.

A manuscript describing her study has been accepted for publication by Medical Education.



Veronica Ho accepting the Australian Prescriber sponsored prize from Professor Gary Rogers, President of ANZAHPE

Janus kinase inhibitors in rheumatoid arthritis

Clinical applications

SUMMARY

Tofacitinib, an oral Janus kinase inhibitor, is an effective treatment for rheumatoid arthritis. Adverse effects are generally mild and include cytopenias and hyperlipidaemia. Opportunistic infections such as herpes zoster may occur with tofacitinib.

Introduction

Despite the advent of biological therapies for rheumatoid arthritis, many patients continue to experience unacceptable levels of disease. Furthermore, biological drugs have to be administered parenterally.

Janus kinase inhibitors are oral drugs. They interfere with signalling through type I and II cytokine receptors which have been shown to be critical in rheumatoid arthritis.¹

Tofacitinib

Tofacitinib is an oral Janus kinase inhibitor with preferential inhibition of Janus kinase 3 and 1 over Janus kinase 2. It has an oral bioavailability of 74% and a mean elimination half-life of approximately three hours. Most (70%) of the drug is metabolised (CYP3A4 predominant) and 30% is renally excreted.²

Tofacitinib 5 mg twice a day has recently been approved by the US Food and Drug Administration for moderate to severe rheumatoid arthritis refractory to disease-modifying treatments.³

Phase II trials

In phase II studies, tofacitinib was superior to placebo when added to methotrexate in patients with rheumatoid arthritis.^{4,5} Responses were observed quickly, often within one week. Furthermore, small numbers of patients were able to switch from adalimumab to tofacitinib without difficulty.⁶ In the initial studies, tofacitinib was tolerable at doses of 5 mg and 10 mg twice daily.

Phase III trials

Several phase III trials have been conducted to assess the efficacy and safety of tofacitinib in patients with rheumatoid arthritis (see Table). The American College of Rheumatology 20 criteria (ACR 20) were used to measure response rates (see Box).

ORAL Solo trial

A six month, double-blind study enrolled 611 patients who had not had an adequate response to at least one non-biological or biological disease-modifying drug. Patients received placebo or tofacitinib 5 mg or 10 mg twice daily in addition to usual care. Antimalarial drugs, non-steroidal anti-inflammatory drugs and glucocorticoids (≤10 mg prednisone/day) were permitted but all other disease-modifying drugs were discontinued for the trial.

A clinical benefit was demonstrated, but there was no significant increase in the number of patients entering remission according to disease activity score criteria.⁷ This suggested that while tofacitinib is effective as a monotherapy, additional disease-modifying therapy may be required.

ORAL Standard trial

Another study assessed tofacitinib as an add-on therapy in patients who had not responded adequately to methotrexate. This was a 12-month study of 717 patients on stable doses of methotrexate. They were given tofacitinib 5 mg or 10 mg twice daily, adalimumab 40 mg every two weeks, or placebo. The study showed similar clinical benefit with the active treatments over placebo as well as an increase in numbers of patients entering remission at six months (based on a disease activity score).⁸

ORAL Step study

Responses among patients with more resistant disease have also been assessed. A six-month study enrolled 399 people who had not responded to at least one tumour necrosis factor inhibitor. Patients were randomised to placebo or tofacitinib (5 mg or 10 mg twice a day). After three months, patients who received placebo were transferred to tofacitinib. Once again, significant improvements were observed in ACR 20 response rates after three months and

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on a disability questionnaire (Health Assessment Questionnaire-Disability Index). However, among these patients with more resistant disease, there was no significant increase in rates of remission.⁹

ORAL Sync study

The ORAL Sync study, reported as a conference abstract, assessed the addition of tofacitinib to treatment in patients who had ongoing disease despite receiving disease-modifying drugs. This trial design is likely to most closely reflect current clinical practice. Again, the study showed an improved response rate and disability score with tofacitinib, and a significant increase in the number of patients achieving remission.¹⁰

Radiological outcomes

More recently, 12-month data looking at radiological outcomes with tofacitinib and methotrexate suggest that tofacitinib inhibits structural progression, both as solo therapy (to a greater level than methotrexate) and with background methotrexate use.^{11,12}

Adverse events

The most common adverse events with tofacitinib were diarrhoea, nasopharyngitis, urinary tract infection, nausea and headache. The risk of infection is an important consideration, although a recent meta-analysis concluded that it was similar to the risk with biological therapies.

There have been 12 cases of tuberculosis reported in the trial cohorts, 11 of whom initially screened negative for the disease. Ten cases occurred in countries endemic for tuberculosis.

The incidence of herpes zoster is also increased with tofacitinib. In a pooled analysis of phase II, III and long-term extension studies (4789 patients with 5651 patient-years of tofacitinib treatment), 239 patients experienced herpes zoster. One case was multidermatomal, none involved visceral dissemination and there were no fatalities.¹³

Pooled analyses favour a 5 mg twice-daily dose of tofacitinib to reduce the risk of serious infection (seen in long-term extension studies). The transient effects of tofacitinib mean that its immunomodulatory effect can be rapidly reversed if sepsis occurs.^{9,14,15}

Hyperlipidaemia has been consistently observed in the trials and may relate to inhibition of interleukin-6 signalling.¹⁴ Atorvastatin appears to reduce the increase in cholesterol,¹⁶ but long-term cardiovascular effects will need to be assessed in the future.

Elevations in liver aminotransferases, neutropenia, thrombocytopenia and anaemia have all been reported. Changes are generally mild. A small rise in serum creatinine has been noted, but at this stage

Table Phase III trials of tofacitinib in rheumatoid arthritis

Trials	Treatment given twice daily	Response rate ACR 20
ORAL Solo trial (3 month end point) ⁷	tofacitinib 5 mg tofacitinib 10 mg placebo	59.8% 65.7% 26.7%
ORAL Standard trial (6 month end point) ⁸	tofacitinib 5 mg tofacitinib 10 mg placebo	51.5% 52.6% 28.3%
ORAL Step study (3 month end point) ⁹	tofacitinib 5 mg tofacitinib 10 mg placebo	41.7% 48.1% 24.4%
ORAL Sync study (6 month end point) ¹⁰	tofacitinib 5 mg tofacitinib 10 mg placebo	52.7% 58.3% 31.2%

ACR 20 American College of Rheumatology response criteria (see Box)

Box Measuring response to treatment in rheumatoid arthritis

The American College of Rheumatology (ACR) response criteria are a standard instrument used in rheumatoid arthritis trials.

The ACR criteria of 20%, 50% or 70% improvement in clinical manifestations are an attempt to quantify response to therapy. Thus, a patient with an ACR 20 response to an intervention has demonstrated a 20% decrease in the combined number of swollen and tender joint counts, and a 20% improvement in any 3 of the 5 core-set measures which include Patient's Global Assessment, Physician's Global Assessment of disease activity (on 10 cm visual analogue scale), Patient's Assessment of Pain score (on 10 cm visual analogue scale), Health Assessment Questionnaire – Disability Index (HAQ-DI), and acute phase reactants (erythrocyte sedimentation rate or C-reactive protein).

The achievement of an ACR 20 response by an individual is considered to be the minimally achieved level of response that is of clinical relevance.

See: www.rheumatology.org

has not been clinically significant.^{14,15} As yet, there has been no reported increase in malignancy, but long-term data are still needed.

Other indications

Tofacitinib has shown promising results in phase II trials in other autoimmune diseases including ulcerative colitis and psoriasis. It is also being assessed as an immunosuppressant in renal transplant recipients.¹⁷⁻¹⁹

Janus kinase inhibitors in rheumatoid arthritis - clinical applications

Conclusion

Tofacitinib is not yet available in Australia, but its release will provide an alternative option and effective oral treatment for patients with rheumatoid arthritis resistant to standard therapy. While initial

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data are promising, longer-term studies are required to better assess the risk of malignancy, opportunistic infection and radiological changes. Other Janus kinase inhibitors are currently undergoing clinical trials for rheumatoid arthritis.³ ◀

Conflict of interest: none declared

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Janus kinase inhibitors in myeloproliferative neoplasms

Clinical applications

SUMMARY

Hyperactive Janus kinase 2 signalling is a key molecular event in polycythaemia, essential thrombocythaemia and myelofibrosis. This is associated with the V617F mutation in the Janus kinase 2 gene of many patients with myeloproliferative disease.

Ruxolitinib is the first Janus kinase inhibitor to be licensed in Australia for the treatment of myelofibrosis.

Ruxolitinib can cause rapid and sustained splenic shrinkage in up to 42% of patients with higher risk myelofibrosis, however it does not change the risk of leukaemic transformation.

Treatment with ruxolitinib can be limited by significant anaemia.

Introduction

It has long been known that the myeloproliferative neoplasms – essential thrombocythaemia, polycythaemia vera and myelofibrosis – share clinical and pathological features. In 2005, a mutation in the Janus kinase 2 gene (V617F mutation) was discovered in more than 95% of patients with polycythaemia vera and approximately 50% of those with essential thrombocythaemia and primary myelofibrosis.¹⁻⁴ Chronic myeloid leukaemia, another myeloproliferative neoplasm, is associated with the presence of a different mutation – the Philadelphia chromosome (BCR-ABL translocation).

The V617F mutation makes the Janus kinase continuously active. As a result, polycythaemia, thrombocythaemia and leukocytosis can develop independently from growth factor regulation. Patients without the mutation also display hyperactive Janus kinase signalling.⁵

Janus kinase inhibitors

Several Janus kinase inhibitors are in clinical trials for myelofibrosis, polycythaemia vera and essential thrombocythaemia. These include ruxolitinib, pacritinib and momelotinib.

Ruxolitinib

Ruxolitinib recently became the first approved Janus kinase inhibitor in Australia for myelofibrosis. It has completed phase III testing and is currently being evaluated in expanded clinical settings including in patients with myelofibrosis and thrombocytopenia (starting platelet count 50–100 x 10⁹/L), and in other

myeloproliferative neoplasms. It is also being assessed in combination with other therapies.

Two randomised phase III trials of ruxolitinib – COMFORT-I and COMFORT-II – were completed in patients with higher risk myelofibrosis, including those with primary or secondary myelofibrosis, irrespective of whether they had the V617F mutation.^{6,7} Splenomegaly is a common cause of disability in patients with myelofibrosis. The primary end point of the studies was a 35% reduction in splenic volume on magnetic resonance imaging.

Outcomes from both studies were remarkably similar. In COMFORT-I, patients with myelofibrosis received oral ruxolitinib 15 or 20 mg twice a day (155 patients) or placebo (154 patients). The starting dose was dependent on the patients' baseline platelet count. After 24 weeks, a 35% reduction in spleen size was achieved in 41.9% of ruxolitinib-treated patients versus 0.7% of placebo-treated patients (p<0.001). COMFORT-II compared ruxolitinib with best available therapy (2:1 ratio). After 48 weeks, 28% of the ruxolitinib-treated patients met the primary end point versus 0% in the best available therapy group (p<0.001).

In both studies, 97% of patients experienced some degree of splenic shrinkage with ruxolitinib therapy. Responses were rapid and sustained and were irrespective of the type of myelofibrosis (primary vs post-polycythaemia vera or post-essential thrombocythaemia), mutation status, initial spleen size or baseline symptoms. Patients on ruxolitinib had an improved quality of life and reversal of disease-related weight loss. Ruxolitinib was effective in patients with

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Janus kinase inhibitors in myeloproliferative neoplasms - clinical applications

the wild-type Janus kinase 2 gene as well as those with the V617F mutation.

At the latest update, both studies showed an improvement in overall survival with ruxolitinib therapy, with hazard ratios of 0.58 (confidence interval (CI) 0.36–0.95) in COMFORT-I⁸ and 0.51 (CI 0.26–0.99) in COMFORT-II⁹. It is likely that the improvement in survival was due to the relief of disease-related symptoms (such as splenic pain, poor appetite and immobility), rather than modification of the underlying disease. In particular, the risk of leukaemic transformation is not reduced. This is unlike the situation with chronic myeloid leukaemia, where treatment with tyrosine kinase inhibitors such as imatinib substantially alters the natural history of the disease, and markedly reduces the risk of progression to acute leukaemia.

The efficacy of ruxolitinib in patients with lower risk disease has not been assessed in randomised trials.

Adverse reactions

The major toxicities of ruxolitinib were anaemia and thrombocytopenia, and to a lesser extent minor bruising (grade 1–2), dizziness, headache and diarrhoea.^{6,7} Significant anaemia (haemoglobin <80 g/L) and thrombocytopenia (<50 x 10^{9} /L) occurred in 40–52% and 10–16% of patients respectively. Experience outside the trials (conference abstracts) suggests that the efficacy and adverse effect profile of ruxolitinib in the real world is similar to that of the COMFORT studies.

Polycythaemia vera and essential thrombocythaemia

Ruxolitinib was studied in a phase II study of patients with either polycythaemia vera (n=34) or essential thrombocythaemia (n=39) who were resistant or intolerant to hydroxyurea therapy.^{10,11} In patients with polycythaemia vera, 97% reached their target haematocrit (≤ 0.45) without phlebotomy, and 61% of patients with splenomegaly had at least a 50% reduction in palpable spleen length. Importantly, most patients experienced a reduction or complete resolution of polycythaemia vera-associated symptoms including pruritus, night sweats and bone pain. For patients with essential thrombocythaemia, 82% had reduced platelets (<600 x $10^{9}/L$) and in 49% the platelet count reduced to normal. Phase III studies of ruxolitinib in polycythaemia vera have completed recruitment.

Conclusion

Janus kinase 2 inhibitors have shown activity in the relief of symptoms associated with myeloproliferative neoplasms and splenomegaly. However, they do not substantially alter the natural history of the disease. Current research aims to develop combination therapies which also inhibit alternative cellular targets.

Conflict of interest: none declared

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Tricks of the trade in drug promotion

Non-propositional content in pharmaceutical advertising to health professionals

SUMMARY

Advertisements for prescription drugs aim to increase use of the products. These advertisements make claims about the drugs, but also include non-propositional content.

The purpose of non-propositional content is to encourage good feelings about the products. This can be achieved with imagery that features happy people, fun activities or pleasing scenery.

Non-propositional content may lead health professionals to believe a drug is more beneficial or safer than the evidence suggests, even though they deny being influenced by advertising.

To avoid being misled by advertising, health professionals could analyse the claims being made and compare them with independent sources of drug information. Ignoring promotional material is another option.

Introduction

Direct-to-consumer advertising of prescription drugs is prohibited in Australia, however drugs are advertised to healthcare professionals. While perhaps not as contentious as direct-to-consumer advertising, promoting drugs to doctors is still controversial.

A common concern is that advertisers, who are paid to persuade, distort information to present a drug favourably. There is evidence that advertisements:

- unduly emphasise benefits over harm¹
- fail to quantify serious risks²
- make claims with inadequate or no substantiation³
- rely heavily on research funded by the drug's manufacturer.⁴

Content of advertisements

The Competition and Consumer Act 2010 places broad constraints on the use of false or misleading representations in advertising.⁵ The Medicines Australia Code of Conduct also states that:

all information, claims and graphical representations provided to healthcare professionals ... must be current, accurate, balanced and must not mislead either directly, by implication, or by omission.⁶

These restrictions mainly apply to the propositional content, which is explicit claims about the drug that can be assessed as true or false (see Box). This propositional content can be checked against independent resources and the product information, which refers to the drug's dose, indications, contraindications, precautions and adverse reactions.⁷ For example, an Australian advertisement for Circadin

(prolonged-release melatonin) stated that it 'delivers quality restorative sleep with no evidence of rebound insomnia, tolerance, dependence or withdrawal symptoms. Patients awake refreshed and ready to face the day'.⁸ Each claim can, in principle, be verified or refuted by looking for supporting evidence.

Drug advertisements also contain non-propositional content, which persuades without conveying a proposition that can be proved true or false (see Box).9 Imagery is a commonly used form of non-propositional content. About half the Circadin advertisement was imagery. There were two pictures of a woman waking up. In the first, her head is barely raised and her eyes are half closed. The light is dim blue and the caption reads '7.00 am'. In the second, the woman is sitting up smiling and holding a cup of coffee. There is bright light and the caption reads '7.00 am: Circadin'. The background to both images is a dark sky that lightens as sun breaks through cloud.⁸ The implication may be that Circadin takes people out of the 'clouds' of insomnia into the 'light' of quality sleep. However, the picture is not just a didactic message. It aims to build positive emotional associations with the drug. To this end, many drug advertisements feature happy people, fun activities

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Propositional content – explicit claims of a product which can be assessed as true or false Non-propositional content – images, music or other things in advertising that persuade, but cannot be judged true or false in the same way that statements or 'propositions' can Evaluative conditioning – creation of a favourable attitude to an object by repeatedly pairing it with something that elicits positive feelings. For example, consumer products are often paired with images of attractive smiling people

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and majestic scenery. This non-propositional content is influential yet often escapes regulation because it is not obviously false or misleading.

Emotion and persuasion

Aristotle recognised the persuasive power of emotion in 'The art of rhetoric'. For Aristotle, to induce feeling or 'pathos' in the audience was as potent a rhetorical tool as the good character of the speaker ('ethos') and the clarity of their argument ('logos'). However, in 'Phaedrus', Plato cast emotion as an unruly horse threatening to upset the chariot of reason. The view of emotion as the enemy of reason was dominant during the Enlightenment period of history and persists widely today. Research, however, suggests that feeling or 'affect' is not only essential for decision making, but actually helps it.

In the USA in 2005 drug companies spent just under half a billion US dollars on journal advertising – this returned approximately five dollars for every dollar invested Theorists now propose an 'affect heuristic' or shortcut by which feelings aid decisions.¹⁰ We unconsciously consider a range of options, tag each with feeling, and are biased to choose the one with the most positive affective reward. In short, we use feelings as information about what is good for us.¹¹

Emotions may be especially useful when dealing with complex problems. People who rely on feelings to weigh many attributes of a new car may make better purchase decisions than others who engage in lengthy deliberation.¹² In a gambling task, people have physiological changes when they are

considering a choice that is risky, before they know it is a risky choice. Non-conscious biases guide their behaviour before their conscious knowledge does.¹³

Evaluative conditioning

Advertisers co-opt our feelings in ways that suit their persuasive goals. Evaluative conditioning is a prominent means by which branding creates positive feelings (see Box).¹⁴ Products for which we hold no special feeling are repeatedly paired with images or music that make us feel good. In a variant of classical conditioning, our good feelings eventually become linked to the product. Evaluative conditioning fosters more positive beliefs about a drug's safety and efficacy, and increases the intention to use it.¹⁵ This process occurs with little or no conscious awareness and the changes in belief are likely to persist.¹⁶

Consistent with drug advertising in the USA, print advertisements in Australian medical publications make copious use of imagery known to cause evaluative conditioning.⁹ Between 60%¹⁷ and 75%¹⁸ of US print direct-to-consumer advertising of prescription medicines includes an emotional appeal in the headline or visuals. Negative emotions such as fear, sadness or shame are associated with the illness or failure to use the drug. Positive emotions such as joy, happiness and humour often signal a return to normality through use of the product.

Emotional appeals are also created by the way promotional claims are worded. An advertisement for the antiplatelet drug ticagrelor urged readers to 'Save even more lives'.¹⁹ Positive words have been shown to produce evaluative conditioning,²⁰ so this phrase is likely to persuade more than simply saying 'Reduce mortality', without being overtly misleading.

Are health professionals vulnerable to evaluative conditioning?

Many health professionals believe their specialised knowledge makes them less vulnerable to emotional persuasion. The 'elaboration likelihood' model gives some support to this view. It proposes that advertisements persuade by a central route that is conscious and deliberative, and by a peripheral route that is unconscious and automatic.²¹ (Note: this model does not refer to the central and peripheral nervous system.) Viewers are more likely to process information via the central route – the path taken by propositional content – if they have the motivation and ability to do so. Health professionals may be more motivated to focus on an advertisement's explicit claims and they clearly have more ability than a layperson to critique the claims.

The peripheral route of persuasion is the path taken by non-propositional content and is increased with distraction and time pressure. Busy doctors may be more vulnerable to this pathway than they think. A study found many doctors' prescriptions reflected commercial rather than academic sources of information, despite their denying the influence of advertising.²² Indeed, health professionals may mirror the wider community in being subject to the 'third person effect'. This is a psychological bias where others are deemed to be more easily persuaded by mass communication than oneself.²³

Advertising in medical journals is effective. In the USA in 2005 drug companies spent just under half a billion US dollars on journal advertising.²⁴ This returned approximately five dollars for every dollar invested.²⁵ There is little doubt that the persuasive intent of drug advertising results in altered prescribing patterns.²⁶

How can health professionals resist?

Two techniques for resisting evaluative conditioning have been analysed.²⁷ 'Persuasion knowledge priming' arms the viewer with an understanding that positive

images bear little relation to a product's attributes and should be ignored. Alternatively, viewers are asked to relabel positive imagery with negative terms. Someone looking at the Circadin advertisement could, for example, try to ignore the smiling woman, or recite unpleasant adverse effects as they view her image. However, these techniques only marginally reduced conditioning in the cited study, and this studied beer rather than pharmaceuticals directly.²⁷

Some researchers consider the peripheral route of persuasion to be 'mental contamination'.²⁸ After reviewing a range of possible techniques, they conclude that reduced exposure to the persuasive stimulus is the only sure way to limit its influence. This means not looking at advertisements for drugs. If you do look at advertisements use an analytical approach. Be aware of the techniques that are being used to encourage prescribing of the product.

Using independent sources of information about drugs and therapeutics, such as *Australian Prescriber*, Australian Medicines Handbook and Therapeutic Guidelines may be beneficial. However, there is no evidence to show that independent sources can overcome the effects of evaluative conditioning.

How should regulators respond?

Regulating only propositional content may not reduce the influence of advertising. The US Food and Drug Administration (FDA) recognises the threat to accurate communication posed by non-propositional content in direct-to-consumer advertising of prescription medicines. In TV commercials it limits the use of distracting imagery when adverse effects are read. In print advertisements it bans 'signalling effects' where benefit information put in a headline has more impact than risks buried in the small print.²⁹ The FDA is even conducting research on how direct-to-consumer advertising of prescription medicines impacts on unconscious or implicit attitudes.³⁰

Calls to mandate statements of absolute risk in drug advertisements also recognise the power of nonpropositional content. In particular, they aim to reduce so called 'framing effects' where the same information takes on different meaning when its format is varied. Stating a relative mortality reduction of, for example, 50% instead of an absolute reduction from 2% to 1%, does not promulgate a falsehood, but it does frame the information to present the treatment most favourably.³¹

Conclusion

Non-propositional content is effective and so it is unsurprising that positive imagery dominates many drug advertisements. If such content instils falsely favourable beliefs, it is doubtful that increased prescribing will benefit public health. Also, if the advertising of medicines to health professionals is to be properly regulated, research that quantifies the persuasive impact of non-propositional content is needed. Until then prescribers should be aware of the techniques of advertising and adopt an analytical approach when looking at advertisements for drugs.

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Book review

Stockley's Drug Interactions, Pocket Companion

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pocket companion

Stockley's Drug Interactions 2014

Edited by Claire L Preston

PP)

Preston CL. Baxter K.

London: Pharmaceutical Press; 2014. 720 pages

This pocket companion is published annually. It is based on the monographs in Stockley's Drug Interactions, which are fully referenced and derived from clinical studies, case reports and systematic reviews.

The book provides a compact text that is quick and easy to access and briefly summarises the evidence for each interaction. There are 2200 monographs listed alphabetically according to the generic name of the individual drugs or drug groups (e.g. ACE inhibitors, NSAIDs). Each monograph has one of four rating symbols assigned to each interaction determined by the action required, the severity or likely effect of an unmanaged interaction, and the extent of the evidence. The symbols identify interactions that:

- need to be avoided
- are potentially hazardous and caution is required
- are possible and may require monitoring
- are not significant and the drugs may be used concomitantly.

The interaction is defined under the two listed drugs. This is followed by a short practical discussion on how the interaction should be managed, the manufacturer's recommendations and guidelines from professional societies. For example, the manufacturer of leflunomide recommends avoiding alcohol while the British Society of Rheumatology limits alcohol intake to four to eight units a week.

One limitation of the book is the indexing. It could be improved as some interactions may be missed especially if the book is relied on as a quick, comprehensive resource. For example, a search for an interaction between voriconazole and simvastatin under voriconazole (which also states to 'see Azoles') will only find fluvastatin listed and not atorvastatin, simvastatin or statins. However, a search under azoles will find atorvastatin and simvastatin but not statins or fluvastatin.

Overall, this pocket companion provides a handy, clear and concise reference for identifying drug interactions and a practical guide to their management.

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Dental note

Topical corticosteroids and the oral mucosa

Topical corticosteroid ointments are an important component in the management of oral mucosal disease. When used appropriately, they are effective and have few adverse reactions. Therapeutic Guidelines: Oral and Dental lists:¹

- the indications for use
- properties of topical corticosteroids used on the oral mucosa
- information on application
- adverse effects, precautions and contraindications.

Oral medicine specialists manage a range of mucocutaneous diseases, either with concurrent skin involvement, or restricted to the oral mucosa. A number of these are T-lymphocyte-mediated and, as such, generally respond well to topical corticosteroid preparations. It is important that topical corticosteroids be used only when a condition that requires their use has been correctly diagnosed. Ointments are the preferred vehicle for delivery of the corticosteroid both for patient acceptance and clinical effectiveness.

Common oral mucosal conditions treated with topical corticosteroid ointments include oral lichen planus and aphthous ulcerative disease. Both respond well to topical corticosteroids, although with different defined end points.

Lichen planus generally has a fluctuating course, often extending over many years, so the aims of treatment include the control of the patient's symptoms. These usually result from atrophic and erythematous lichen planus. Minimisation of the flares of this condition can generally be achieved by the judicious use of topical corticosteroids. The aim with aphthae is to inhibit lesion development past the prodromal, preulcerative phase or at least to significantly truncate the clinical course of developed lesions in the ulcerative phase.

Concerns with the use of medium and high potency corticosteroid preparations on the oral mucosa relate to effectiveness in a wet environment and atrophy with inappropriate prolonged use. As with any medication, clear instruction to the patient is important. Drug uptake is rapid even in a wet environment and with careful and frugal application, even over a prolonged period of time, adverse effects are extremely uncommon. The main concern with corticosteroid use is a secondary candidosis in predisposed patients such as those with salivary hypofunction, prosthesis wearers, users of inhaled corticosteroids and those taking antibiotics.

Experience shows that use of low potency corticosteroids is often ineffective. Medium and variably high potency corticosteroid ointments provide the most efficacious outcomes for oral mucosal diseases.

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Medicines Safety Update

Volume 5, Number 5, October 2014

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Bupropion and serious cardiovascular adverse events

The Product Information for bupropion is being updated to provide further information about the risk of serious cardiovascular adverse events.

Bupropion is a selective inhibitor of the neuronal reuptake of catecholamines, noradrenaline and dopamine. It is registered for use in Australia as a short-term adjunctive therapy, used in conjunction with counselling and abstinence, for nicotine dependence to assist in smoking cessation.

The Product Information (PI) for bupropion had previously contained information regarding hypertension. However, the TGA has identified postmarket spontaneous reports of more serious cardiovascular events, including myocardial infarction. To address this, the TGA is working closely with the innovator sponsor to update and strengthen the precautions for serious cardiovascular adverse events in the PI.

Information update

The updated information will advise that there have been reports of patients receiving bupropion (alone and in combination with nicotine replacement therapy) experiencing severe hypertension requiring acute treatment, in patients both with and without pre-existing hypertension.

The updated information will also advise that there is limited clinical experience establishing the safety of bupropion in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, health professionals should exercise care if using bupropion in such patients.

It is recommended that blood pressure be monitored while the patient is taking bupropion, especially in patients with pre-existing hypertension, and consideration be given to discontinuing treatment if a clinically significant increase is observed.

A higher rate of hypertension has been observed when treatment with bupropion is combined with use of nicotine transdermal system products (patches).

If bupropion is used in combination with nicotine patches, caution must be exercised and weekly monitoring of blood pressure is recommended.

Adverse events

As at 1 July 2014, the TGA has received a number of cardiovascular adverse event reports associated with use of bupropion. This includes 24 reports of myocardial infarction, five reports of cerebrovascular accident, and one report of transient ischaemic attack.

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



Methylphenidate and priapism

Health professionals are advised that in very rare cases treatment with methylphenidate may potentially lead to prolonged and sometimes painful erections (priapism).

Methylphenidate is a central nervous system stimulant and is indicated for the treatment of attention deficit hyperactivity disorder (ADHD). It is marketed in Australia as Ritalin and Concerta.

A US Food and Drug Administration review of methylphenidate products resulted in priapism being added as a class warning to the drug's labelling. Subsequent investigation by the TGA found that, while there had been no reports of this adverse event in Australia, the risk of untreated priapism was potentially serious.

A precaution for priapism has recently been added to the Product Information (PI) for methylphenidate.

While this risk applies to all use in males, the greatest concern is regarding pre-pubertal boys, who might not recognise the problem or may be too embarrassed to seek help if it occurs. Health professionals should consider educating parents and caregivers of pre-pubertal boys being treated with methylphenidate about this issue, while reassuring them that it is very rare.

Priapism can develop some time after starting the drug, often following an increase in dose, and has also been observed during a period of methylphenidate withdrawal.

Health professionals who are considering switching patients to another drug due to this issue are advised that atomoxetine, which is also used to treat ADHD, has been associated with priapism. The PI for atomoxetine lists painful or prolonged erection and male genital pain as potential, but very rare, adverse events.

Propranolol – prescribing to patients who may be at risk of self-harm

A recent case investigated by the Coroners Court of Victoria has prompted a warning regarding prescribing propranolol for patients who are suspected of being at risk of self-harm.

Propranolol is a beta-adrenoreceptor blocking drug which has a number of indications, the most common of which are:

- angina pectoris
- hypertension
- prevention of migraine
- essential tremor, including familial and senile tremor
- management of some cardiac dysrhythmias.

Propranolol is available in Australia in 100-tablet pack sizes of 10 mg and 40 mg tablets, as well as a 50-tablet pack of 160 mg tablets. If repeats are provided with a prescription for propranolol, the patient could accumulate a large number of tablets at one time. The coroner recommended that the TGA advise health professionals to exercise caution when prescribing propranolol for patients suspected of being at risk of self-harm, particularly by overdose. Overdosage of propranolol can result in bradycardia, hypotension, bronchospasm and/or acute cardiac failure.

If propranolol is prescribed, consider providing prescriptions for smaller quantities or make other arrangements to reduce the amount of the drug that the patient has access to at one time.

Adverse events

From 1972 to 1 July 2014, the TGA has received 829 reports of adverse events involving propranolol. Of these reports, five involved overdose and/or intentional overdose. Two of these cases resulted in the patient's death.

Health professionals are encouraged to report to the TGA all suspected adverse events relating to propranolol, particularly if they involve overdose and potential self-harm.

Valproate – fetal exposure and cognitive impairment

The TGA has reviewed updated information regarding the association between use of valproate during pregnancy and cognitive impairment in children.

Valproate is an anticonvulsant that is indicated for the treatment of primary generalised epilepsy and partial epilepsy. It is also indicated for the treatment of mania, where other therapy has proven inadequate or is inappropriate.

Earlier studies examined the effect of fetal exposure to valproate on cognitive outcomes in children and these risks are reflected in the Product Information (PI).

In particular, an interim analysis by the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study had found that fetal exposure to valproate was associated with a range of cognitive deficits at three years of age. In 2013, the NEAD study published its final analysis, which found fetal valproate exposure had dose-dependent associations with reduced cognitive abilities across a range of domains at six years of age.¹

Meanwhile, another study found a link between use of valproate during pregnancy and autism spectrum disorders and childhood autism in the offspring, even after adjusting for maternal epilepsy.²

NEAD study

The NEAD study was a prospective observational study that aimed to determine how fetal exposure to different antiepileptic drugs affected cognitive outcomes at various ages. Pregnant women with epilepsy receiving antiepileptic drug monotherapy were enrolled in the study, and their children's IQs were measured at 2, 3, 4.5 and 6 years of age.

There were 305 mothers and 311 live births included in the primary analysis, and 221 mothers and 225 children were included in the age six analysis.

Children with fetal exposure to valproate demonstrated reduced IQ at six years of age compared with other antiepileptic drugs. An increased valproate dose was associated with a range of cognitive deficits, including decreased verbal IQ. While the mean valproate IQ was in the normal range, the 7-10 IQ point reduction for this drug compared with other antiepileptic drugs observed in the study was considered clinically significant.

Autism study

Christensen et al. conducted a population-based cohort study on the risk of autism in children exposed to prenatal valproate.

Of 655 615 children born in Denmark between 1996 and 2006, 5437 were identified with autism spectrum disorder, including 2067 with childhood autism. The estimated absolute risk after 14 years of follow-up was 1.53% (95% confidence interval [CI] 1.47–1.58%) for autism spectrum disorder and 0.48% (95% CI 0.46–0.51%) for childhood autism. Overall, the 508 children exposed to valproate had an absolute risk of 4.42% (95% CI 2.59–7.46%) for autism spectrum disorder (adjusted hazard ratio [HR] 2.9 [95% CI 1.7–4.9]) and 2.50% (95% CI 1.30–4.81%) for childhood autism (adjusted HR 5.2 [95% CI 2.7–10.0]).

Information update

The PI for valproate contains a warning about autism spectrum disorders and information about fetal exposure and the risk of developmental delay in the Use in Pregnancy section. However, the TGA's review of the updated information in the NEAD study has found that the information about cognitive impairment should be updated to show that cognitive deficits have been observed at six years of age.

The sponsor has agreed to update the PI and intends to incorporate any recommendations that may result from an ongoing review being conducted in the European Union.³

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Medicine shortages information resource

Drug shortages can have significant implications for the quality use of medicines and, in rare cases, can be a risk to public health.

Launched in May 2014, the Medicine Shortages Information Initiative aims to improve the communication and management of drug shortages in Australia.

In partnership with Medicines Australia and the Generic Medicines Industry Association, the TGA is providing information to assist health professionals and their patients when there is a temporary or permanent disruption (discontinuation) to the supply of a drug.

Changes to the access of any drug, even when a substitute medicine or therapeutic alternative is available, can have serious impacts.

You and your patients can search the Medicine Shortages Information Initiative website at www.tga.gov.au/hp/information-msi.htm for information about the nature, anticipated duration and status of prescription drug shortages.

The predicted shortage start and end dates are included on the website as soon as the TGA receives the information from the sponsor. In most cases, this will be sufficient to help you and your patients during a shortage period.

Once the shortage is resolved, it will be displayed in the 'Resolved' area for a period of three months.

In extreme cases, the TGA has a number of regulatory options to assist your patients, including the supply of a substitute medicine or therapeutic alternative through the Special Access Scheme. Where it is in the interests of public health, the TGA can also authorise the supply of an otherwise unapproved medicine.

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New drugs

Aclidinium bromide

Approved indication: chronic obstructive pulmonary disease

Bretaris Genuair (A Menarini) 375 microgram as dry powder for inhalation Australian Medicines Handbook section 19.1.2

The treatment of chronic obstructive pulmonary disease aims to relieve symptoms and prevent deterioration. Patients whose symptoms are not relieved by short-acting bronchodilators are usually given maintenance treatment with a long-acting bronchodilator. This could be a beta agonist or an anticholinergic. Aclidinium adds to the choice of inhaled long-acting anticholinergic drugs. It is a muscarinic receptor antagonist which mediates airway smooth muscle contraction.

A multidose device is used to deliver aclidinium powder. (The metered dose is 400 microgram. This delivers 375 microgram of aclidinium bromide from the mouthpiece, which is equivalent to 322 microgram of aclidinium.) After inhalation, the forced expiratory volume in one second (FEV,) increases within 30 minutes. The peak effect is reached within three hours and bronchodilation is sustained for 12 hours. A twice-daily dose is therefore recommended. The peak plasma concentration is reached within 15 minutes and very little aclidinium reaches the systemic circulation as it is rapidly hydrolysed. Most of the metabolites are excreted in the urine, but renal impairment is unlikely to have a clinically significant effect on clearance. Similarly no dose adjustment is recommended for people with liver disease.

In a phase II trial aclidinium bromide 400 microgram (twice daily) was compared with placebo and tiotropium 18 microgram (once daily) in 30 smokers or ex-smokers with chronic obstructive pulmonary disease. Each patient inhaled each treatment for 15 days with a washout period between each course. The mean baseline FEV, was 1.5 L. After 15 days the morning pre-dose FEV, had increased by 143 mL with aclidinium, 107 mL with tiotropium, and decreased by 43 mL with placebo.¹

A larger trial randomised 561 patients to inhale aclidinium or placebo twice daily for 12 weeks. These patients had FEV₁ values between 30% and 80% of their predicted value. At the start of the study the mean FEV₁ was 1.36 L, which was approximately 47% of the predicted value. The primary outcome of the trial was the change in FEV₁ measured just before the morning dose (trough value). After 12 weeks the trough FEV₁ had increased by 62 mL with aclidinium 200 microgram and by 99 mL with 400 microgram. The mean trough FEV₁ in the placebo group declined by 25 mL. Treatment with aclidinium also improved the patients' peak FEV₁ significantly more than placebo.²

Another trial compared aclidinium 200 and 400 microgram twice daily with placebo over 24 weeks. The 828 smokers and ex-smokers in the study had FEV₁ values less than 80% of the predicted value. At baseline the mean FEV₁ was about 53% of the predicted value. After 24 weeks the trough FEV₁ was 99 mL higher than placebo with aclidinium 200 microgram and 128 mL higher with 400 microgram. The peak FEV₁ was 185 mL greater than placebo with aclidinium 200 microgram and 209 mL greater with 400 microgram (see Table).

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.

Some of the views

Table Efficacy of aclidinium bromide in chronic obstructive pulmonary disease ³

	Aclidinium 400 microgram twice daily	Placebo
Number of patients	272	276
Baseline mean FEV,	1.51 L	1.5 L
Change in FEV, after 24 weeks trough peak	55 mL 231 mL	-73 mL 22 mL
Overall rate of exacerbations/patient/year	0.4	0.6
Rate of moderate or severe exacerbations/patient/year	0.34	0.47
FEV, forced expiratory volume in one second		

There were also improvements in symptoms, and patients taking aclidinium needed to use a shortacting bronchodilator for relief less often than patients taking placebo. As the effect of aclidinium was greater at the higher dose, 400 microgram twice daily is the recommended dose.³

Some of the adverse effects, such as dry mouth, can be predicted from the anticholinergic actions of aclidinium. Patients with narrow angle glaucoma, bladder outflow obstruction or unstable cardiac disease were excluded from the trials because of the potential for acute glaucoma, urinary retention and arrhythmia. A few patients had prolongation of the QTc interval on the ECG.³ Adverse events which were more frequent with aclidinium than with placebo included headache, nasopharyngitis and diarrhoea.

The 24-week trial showed that aclidinium has an advantage over placebo. However, most of the advantage in lung function was because of the deterioration of trough FEV₁ in the placebo group. After 24 weeks of treatment with aclidinium 400 microgram twice daily the increase in trough FEV₁ from baseline was 55 mL (see Table).³ While improving symptoms is an important part of the management of chronic obstructive pulmonary disease, not all patients will benefit from aclidinium. A clinically significant improvement was seen in 57% of the patients taking aclidinium compared with 41% of the placebo group. Although aclidinium reduced the rate of exacerbations, the reduction in moderate or severe exacerbations was not statistically different from placebo (see Table).³

What is needed now is a comparison of the effectiveness of the inhaled long-acting anticholinergic bronchodilators in chronic obstructive pulmonary disease. The phase II study showed some advantages for twice-daily aclidinium over oncedaily tiotropium, but the study was too small and the duration too short to show if one drug and device was more effective than the other.¹ Aclidinium bromide is not indicated for asthma.

T manufacturer did not respond to request for data

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First published online 13 August 2014

Updated version published online 3 September 2014

Brentuximab vedotin

Approved indication: Hodgkin lymphoma, anaplastic large cell lymphoma Adcetris (Takeda) vials containing 50 mg powder for injection Australian Medicines Handbook section 14.2.1

Brentuximab vedotin consists of an anti-CD30 antibody conjugated to a cytotoxic drug called monomethylauristatin E (MMAE). The cytotoxic part disrupts the microtubule network in cells and causes apoptosis. This drug is indicated for patients with relapsed or refractory classic Hodgkin lymphoma (including after autologous stem cell transplant) and systemic anaplastic large cell lymphoma. CD30 is selectively expressed on the surface of lymphoma cells in both of these diseases.

Maximum concentrations of the antibody-drug conjugate are reached at the end of a 30-minute intravenous infusion and its terminal half-life is 4–6 days. The antibody portion is thought to be catabolised and a fraction of the cytotoxic portion – MMAE – is metabolised and excreted in the urine and faeces. A lower starting dose should be considered in patients with hepatic impairment or severe renal impairment and close monitoring is recommended.

The anti-CD30 antibody on its own has minimal efficacy – in a trial of 72 people with relapsed or refractory CD30-positive lymphomas, only six responded.¹ However, conjugating the antibody to a cytotoxic drug improved antitumour activity. In a single-arm, open-label phase II trial, 75% of patients with relapsed or refractory Hodgkin lymphoma responded to brentuximab vedotin (see Table).² All of these patients had previously had an autologous transplant. In a similarly designed trial in relapsed or refractory systemic anaplastic large cell lymphoma, 86% of patients had a response to brentuximab vedotin (see Table).³ Just over a quarter of the participants had previously had an autologous transplant.

Infection was the most common adverse event in the trials, occurring in 61% of people. In 16% of cases, infection was thought to be related to the study drug. Serious infections included pneumonia, staphylococcal bacteraemia, sepsis and herpes zoster. The opportunistic infections *Pneumocystis jirovecii* pneumonia and oral candidiasis also occurred.

The most common drug-related adverse effects included peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhoea (34%), neutropenia (21%) and vomiting (20%). Some of these were serious – neutropenia and peripheral sensory neuropathy resulted in delayed or reduced

	Intravenous brentuximab vedotin 1.8 mg/kg every 3 weeks ‡		
Patient response	Hodgkin lymphoma (102 patients)	Refractory systemic anaplastic large cell lymphoma (58 patients)	
Complete remission	34% (35 patients)	57% (33 patients)	
Partial remission	40% (41 patients)	29% (17 patients)	
Stable disease	22% (22 patients)	3% (2 patients)	
Progressive disease	3% (3 patients)	5% (3 patients)	
Not evaluable	1% (1 patient)	2% (1 patient)	
Median duration of complete responses	20.5 months	13.2 months	
Median progression-free survival	5.6 months	13.3 months	
Median overall survival	22.4 months	not reached	

Table Efficacy of brentuximab vedotin in two trials ^{2,3}

‡ patients could have up to a maximum of 16 infusions

dosing. Other serious drug reactions included thrombocytopenia, constipation, diarrhoea, vomiting, fever, peripheral motor neuropathy, hyperglycaemia, demyelinating polyneuropathy, tumour lysis syndrome and Stevens-Johnson syndrome.

Some adverse events were fatal including sepsis, acute pancreatitis and progressive multifocal leukoencephalopathy. Treatment should be stopped if any of these are suspected.

Anaphylaxis has been reported to occur during and after the infusion. This was more common in people with antibodies to the study drug (approximately a third of patients).

Co-administration of strong inhibitors of cytochrome P450 (CYP) 3A4 and P-glycoprotein (e.g. ketoconazole) increases exposure to MMAE so may increase the risk of adverse effects such as neutropenia. The concomitant use of brentuximab vedotin with bleomycin causes pulmonary toxicity and is contraindicated.

Brentuximab vedotin has the potential to cause fetal harm and is not recommended during pregnancy. There are no data for its use during lactation. Animal toxicity studies indicated that this drug may affect reproductive function and fertility in males. Men are advised to have sperm frozen before treatment and avoid fathering a child during and for six months after treatment.

Brentuximab vedotin seemed to be effective in advanced Hodgkin lymphoma and anaplastic large cell lymphoma, with 34–57% of patients achieving complete remission. However, the trials were small and there were no comparators. Adverse effects can be severe and sometimes fatal and are likely to limit treatment dose and duration. There are no safety data for this drug beyond 12 months of treatment.

T manufacturer provided the AusPAR

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First published online 30 July 2014

Dolutegravir

Approved indication: HIV infection

Tivicay (ViiV Healthcare) 50 mg film-coated tablets Australian Medicines Handbook section 5.5.4

Integrase inhibitors, such as elvitegravir and raltegravir, can be used in combination with other antiretroviral drugs to treat HIV infection. Dolutegravir also inhibits HIV integrase to disrupt viral replication. Unlike raltegravir, dolutegravir can be given once daily and unlike elvitegravir it does not need 'boosting' with other drugs to have an effect.

Dolutegravir is rapidly absorbed and although food has some effect on bioavailability it is not clinically significant. The drug's distribution includes the genital tract and cerebrospinal fluid. It is metabolised in the liver with most of the dose being excreted in the faeces. No dose adjustment is required in patients with renal impairment or mild-moderate liver impairment. The half-life is approximately 14 hours.

A combination of once-daily dolutegravir with abacavir and lamivudine was compared to a combination of efavirenz, tenofovir and emtricitabine. The 844 adults in the trial had not previously been treated for HIV and had viral RNA exceeding 1000 copies/mL. After 48 weeks, 88% of the patients who took the dolutegravir combination had less than 50 copies/mL. This was statistically superior to the 81% of patients who responded to the other combination. CD4 lymphocyte counts increased by an average of 267/microlitre with dolutegravir and by 208/microlitre in the control group. This difference was also significant.¹

Another trial of previously untreated patients compared dolutegravir with raltegravir. The 827 adults were randomised to take the integrase inhibitors with combinations of tenofovir/emtricitabine or abacavir/ lamivudine. After 48 weeks there was no significant difference between the groups. The target of less than 50 copies/mL of viral RNA in the plasma was achieved by 88% of the dolutegravir group and 85% of the raltegravir group. Both drugs increased the CD4 lymphocyte count by a median of 230 cells/microlitre.²

Dolutegravir and raltegravir have also been compared in patients with resistance to two or more classes of antiretroviral drugs. None of the 724 adults in the trial had previously received an integrase inhibitor. After 48 weeks, 71% of the patients treated with a regimen containing dolutegravir had plasma viral RNA concentrations below 50 copies/mL. This was statistically superior to the 64% success rate with regimens containing raltegravir. CD4 lymphocytes increased by a mean of 162 cells/microlitre with dolutegravir and 153 cells/microlitre with raltegravir. Resistance to the integrase inhibitors emerged in 1% of the dolutegravir group and 5% of the raltegravir group.³

Dolutegravir is also being studied in patients who are infected with HIV that is resistant to raltegravir or elvitegravir. Data from 183 patients treated for 24 weeks show that in 69% dolutegravir reduced viral RNA to below 50 copies/mL. The response rate varies depending on which genetic mutation is responsible for the viral resistance. A twice-daily dose of dolutegravir is recommended when there is resistance to integrase inhibitors.

There are insufficient data to guide the use of dolutegravir in children under 12 years old. The effect of dolutegravir in pregnancy is also unknown, but it did cross the placenta in animal studies.

Adverse events in patients infected with HIV may be caused by the treatment or the disease itself. When multiple drugs are used it can be difficult to determine which one is causing an adverse event. Some problems such as immune reconstitution syndrome may be associated with any retroviral therapy. In the studies which compared dolutegravir and raltegravir there were similar adverse effects.^{2,3} These include diarrhoea, nausea and headache. Rashes may be a sign of hypersensitivity. As hypersensitivity reactions may also affect the liver, liver function should be checked.

Dolutegravir will be used in combination with other antiretroviral drugs. While there are some interactions these may not require dose adjustment. Efavirenz reduces dolutegravir concentrations so this combination should be avoided or a twice-daily dose of dolutegravir will be needed. Antacids containing magnesium, aluminium or calcium should not be taken within several hours of dolutegravir as they reduce its absorption. The combined oral contraceptive pill and methadone do not have a significant interaction with dolutegravir.

Adherence to treatment is very important in managing HIV infection. An effective once-daily drug will help adherence and it is likely that dolutegravir will be formulated with other drugs to allow patients to take a single daily dose of all their drugs. When used in previously untreated patients viral resistance to dolutegravir did not seem to be a problem.^{1,2} This may give it another advantage over other integrase inhibitors, but the development of resistance will need to be monitored once dolutegravir is more widely used.

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First published online 27 June 2014

Obinutuzumab

Approved indication: chronic lymphocytic leukaemia

Gazyva (Roche)

1000 mg/40 mL concentrate solution for infusion Australian Medicines Handbook section 14.2.1

Chronic lymphocytic leukaemia is the most common leukaemia in adults and usually occurs in older age. It is characterised by an accumulation of abnormal B lymphocytes and median survival is 8–10 years. Current treatments include chlorambucil, cyclophosphamide, fludarabine, alemtuzumab (Aust Prescr 2006;29:167–71) and rituximab.

Obinutuzumab is a humanised monoclonal antibody. Like rituximab, it is specific for the CD20 transmembrane antigen on the surface of B lymphocytes. Binding of obinutuzumab to this antigen is thought to cause cell death by antibodydependent phagocytosis and cellular cytotoxicity.

In a randomised open-label study, obinutuzumab added to chlorambucil was investigated in 781 previously untreated people with chronic lymphocytic leukaemia who required treatment. They had enlarged lymph nodes or spleen, thrombocytopenia and anaemia, or symptomatic disease.¹ Their median age was 73 years (39–90 years) and their median creatinine clearance was 62 mL/minute. Most of the patients had more than three comorbidities – vascular, cardiac, nutritional, gastrointestinal and metabolic disorders were the most common.

Patients were randomised into three treatment groups – chlorambucil plus obinutuzumab, chlorambucil plus rituximab, and chlorambucil alone. One arm of the trial compared chlorambucil and obinutuzumab with chlorambucil alone and the other arm compared chlorambucil and obinutuzumab with chlorambucil and rituximab. Patients receiving chlorambucil alone whose disease progressed during or after treatment were allowed to cross over to the chlorambucil plus obinutuzumab group.

Treatment was given in six 28-day cycles. The first cycle consisted of an intravenous infusion of obinutuzumab 1000 mg on days 1, 8 and 15. In the next five cycles obinutuzumab was only given on day 1. Chlorambucil was given on day 1 and 15 in all treatment cycles.

After six cycles of treatment, obinutuzumab plus chlorambucil prolonged progression-free survival by 15 months compared to chlorambucil alone, and by 11 months compared to rituximab plus chlorambucil. More patients had a complete or partial response to the obinutuzumab combination than to chlorambucil alone (see Table). Median overall survival times in the trial were not reached.¹

The most common adverse events with obinutuzumab were infusion-related reactions. These occurred in two-thirds of people, mostly during the first infusion, and included nausea, chills, hypotension, fever, vomiting, dyspnoea, flushing, hypertension, headache, tachycardia and diarrhoea. Bronchospasm, throat irritation, wheezing and atrial fibrillation also occurred. To reduce infusion reactions, giving the first obinutuzumab infusion slowly in two doses over two days is recommended. Also, antihypertensive drugs should be withheld 12 hours before the infusion and one hour after. Although premedication with a corticosteroid, analgesic and antihistamine is also recommended, it only modestly reduced infusion-related reactions in the trial.¹ As tumour lysis syndrome has also been reported, prophylactic allopurinol and adequate hydration before the infusion are recommended for people with a high tumour burden or high lymphocyte count.

Other common adverse events with obinutuzumab included neutropenia (41% of people) and thrombocytopenia (15.4%). Some patients may need granulocyte colony-stimulating factor for their neutropenia.

Infections are common with obinutuzumab (38% of people). The drug should not be given during an active infection and caution is urged in patients with a chronic or recurring infection. Fatal cases of progressive multifocal leukoencephalopathy have been reported with obinutuzumab and patients with neurological symptoms require further investigation. Hepatitis B virus reactivation has also occurred and has been fatal in some cases. Patients should be screened before starting treatment and carriers of the hepatitis B virus should be monitored during and

Table Efficacy of obinutuzumab added to chlorambucil in chronic lymphocytic leukaemia¹

	Comparison 1		Comparison 2	
	Chlorambucil plus obinutuzumab	Chlorambucil alone	Chlorambucil plus obinutuzumab	Chlorambucil plus rituximab
Number of patients	238	118	333	329
Estimated median progression-free survival	26.7 months	11.1 months	26.7 months	15.2 months
Patients with a complete response‡	22.3%	0%	20.7%	7%
Patients with a partial response‡	55%	31.4%	57.7%	58.1%

‡ response was measured three months after the end of six treatment cycles

for at least 12 months after treatment. Obinutuzumab should be discontinued if hepatitis develops. Live vaccines are not recommended.

Worsening heart problems such as arrhythmias, angina, acute coronary syndrome, myocardial infarction and heart failure have occurred with this drug. Some cases resulted in death. Patients with a pre-existing heart condition should be closely monitored, especially during infusions.

After infusion, obinutuzumab is cleared by catabolism. After six cycles of treatment, the elimination half-life is approximately 30 days. Some patients developed antibodies to obinutuzumab (8/140). This did not seem to affect their clinical response and they did not develop anaphylactic or hypersensitivity reactions.

Obinutuzumab appears to benefit patients with chronic lymphocytic leukaemia. However, infusionrelated reactions are common so prophylactic measures are recommended. Fatal infections, including progressive multifocal leukoencephalopathy, have also occurred and patient monitoring is important. It is not yet known if obinutuzumab will prolong overall survival compared to other treatments.

TTT manufacturer provided clinical evaluation

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First published online 13 August 2014

Sofosbuvir

Approved indication: hepatitis C Sovaldi (Gilead) 400 mg tablets

Australian Medicines Handbook section 5.4

There are six major types of hepatitis C – genotypes 1–6. In Australia, about half of cases are caused by genotype 1, a third by genotype 3 and 5% by genotype 2. Until recently, standard treatment for chronic hepatitis C infection was with peginterferon and ribavirin. Protease inhibitors boceprevir (Aust Prescr 2012;35:102-3) and telaprevir (Aust Prescr 2012;35:128-35) were approved in 2012. Adding either of these to peginterferon and ribavirin seems to improve the response rates in people with genotype 1 disease.

Sofosbuvir is another antiviral drug that can be added to combination treatment for chronic hepatitis C. It is a direct-acting nucleotide polymerase inhibitor. The prodrug is converted to a nucleotide analogue in hepatocytes. This active analogue then binds to RNA polymerase which terminates RNA synthesis and inhibits viral replication.

Sofosbuvir 400 mg/day has been investigated in four pivotal phase III hepatitis C trials (see Table).^{1,2} One trial enrolled people with genotypes 1, 4, 5 or 6 and the others enrolled those with genotypes 2 or 3. Some patients in the trials had evidence of liver cirrhosis (15-35%). The primary outcome was the proportion of patients who had achieved a sustained virologic response, defined as undetectable viral RNA 12 weeks after the end of treatment. The highest rate of response to treatment was seen when sofosbuvir was added to peginterferon and ribavirin (90%) in previously untreated patients with genotypes 1, 4, 5 or 6. Response rates were high with all genotypes although there were only seven people with serotypes 5 or 6.1 When sofosbuvir was added to ribavirin in patients with genotypes 2 or 3, response rates in genotype 3 infections were considerably lower than those in genotype 2 infections.^{1,2} Liver cirrhosis was also associated with lower response rates, particularly in those with genotype 3 disease (see Table).

Another trial found that extending sofosbuvir plus ribavirin treatment from 12 to 24 weeks improved response rates in people with genotype 3 infection from 27% (3/11) to 85% (213/250).³ However, as the trial design was changed during the study, there was no hypothesis testing or statistical comparisons and results were only descriptive. Other trials have found that patients co-infected with HIV⁴ and those with hepatocellular carcinoma awaiting liver transplant benefit from treatment with sofosbuvir added to ribavirin.

Treatment discontinuation because of an adverse event occurred in 2% or less of patients taking sofosbuvir-containing regimens. The most common adverse events with sofosbuvir added to ribavirin were fatigue (30–38%), headache (24–30%), nausea (13–22%) and insomnia (15–16%). These events occurred more frequently in patients who were also receiving peginterferon. This was also the case for anaemia and neutropenia.

Absorption is rapid after an oral dose of sofosbuvir with peak plasma concentrations reached after 0.5–2 hours. After metabolism in the liver, most of the dose is excreted in the urine (80%) and faeces (14%). The mean terminal half-life of the main metabolite is 27 hours.

Sofosbuvir is a substrate of P glycoprotein so potent inducers of this transporter, such as rifampicin and St John's wort, should be avoided as they may decrease sofosbuvir's therapeutic effect. Other drugs that may reduce sofosbuvir exposure and are not recommended include modafinil, carbamazepine, phenytoin, phenobarbitone and tipranavir in combination with ritonavir.

Sofosbuvir should always be used in a combination regimen. As ribavirin is teratogenic, adequate contraception must be used during and for six months after treatment in men and women.

Sofosbuvir is effective and well tolerated when added to current therapy for people with chronic hepatitis C. The main predictors of response are viral genotype and liver cirrhosis. Response rates in people with genotype 3 infection are lower than with other genotypes and these people may need to take treatment for longer. Sofosbuvir also provides an alternative for people who

have relapsed, cannot tolerate or do not want to take interferon-containing regimens.

T manufacturer provided the product information

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Table Efficacy of sofosbuvir in chronic hepatitis C infection

Trial name and details	Treatment arms (including duration)	Proportion of patients with a sustained virologic response ‡
NEUTRINO ¹ Single arm, open-label trial in treatment-naïve patients with genotypes 1, 4, 5 and 6 [§]	Sofosbuvir plus peginterferon and ribavirin (12 weeks)	Overall: 90% (295/327) liver cirrhosis: 80%
FISSION ¹ Non-inferiority, randomised, open-label trial in treatment-naïve patients with genotypes 2 or 3 [§]	Sofosbuvir plus ribavirin (12 weeks)	Overall: 67% (170/253) liver cirrhosis: 47% genotype 2: 97% genotype 3: 56%
	Peginterferon plus ribavirin (24 weeks)	Overall: 67% (162/243) liver cirrhosis: 38% genotype 2: 78% genotype 3: 63%
POSITRON ² Randomised, placebo-controlled trial in patients with genotypes 2 or 3 who were intolerant or had refused interferon-containing regimen, or had contraindicated comorbidities [§] FUSION ² Randomised, actively-controlled trial in patients with genotypes 2 or 3 who had relapsed or not responded to previous interferon-containing regimen #	Sofosbuvir plus ribavirin (12 weeks)	Overall: 78% (161/207) genotype 2: 93% genotype 2/liver cirrhosis: 94% genotype 3: 61% genotype 3/liver cirrhosis: 21%
	Placebo (12 weeks)	Overall: 0% (0/68)
	Sofosbuvir plus ribavirin (12 weeks) then placebo (4 weeks)	Overall: 50% (50/100) genotype 2: 86% genotype 2/liver cirrhosis: 60% genotype 3: 30% genotype 3/liver cirrhosis: 19%
	Sofosbuvir plus ribavirin (16 weeks)	Overall 73% (69/95) genotype 2: 94% genotype 2/liver cirrhosis: 78% genotype 3: 62% genotype 3/liver cirrhosis: 61%

[‡] undetectable viral RNA 12 weeks after the end of treatment 35% of enrolled patients had liver cirrhosis

[§] up to 21% of enrolled patients had liver cirrhosis

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

- * At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov)
- At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu)
- A 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)

Corrections

Self-monitoring of blood glucose in type 2 diabetes

Aust Prescr 2010;33:138-40

The statement about frequency of testing should read 'four times a week' and not 'four times a day'.

New drugs: macitentan

Aust Prescr 2014;37:139-43

The 3 mg dose has been deleted as the company advised that only the 10 mg dose is available.

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