Australian Prescriber

AN INDEPENDENT REVIEW

nps.org.au/australianprescriber

August 2018
Volume 41 Number 4

NPS MEDICINEWISE

CONTENTS

EDITORIAL

Fast-tracking of new drugs: getting the balance right

Paul Kubler
Rheumatologist and Clinical pharmacologist, Royal Brisbane and Women's Hospital

Keywords
drug regulation, product approval

Aust Prescr 2018;41:98–9
https://doi.org/10.18773/austprescr.2018.032

In Australia, like the rest of the world, patients and their doctors have a growing desire to access new drugs as soon as possible. They hope to make an impact on conditions with limited pharmacotherapeutic options, such as cystic fibrosis and rare cancers like mesothelioma. New approaches to more common diseases, such as lung cancer and dementia, may offer greater efficacy or less toxicity than current therapies. The pharmaceutical industry is also hungry for expedited drug approvals as a vehicle to reward and encourage innovation. Faster approvals may increase company profits as products get to the market more rapidly.

In 2015, new drug approvals in Australia by the Therapeutic Goods Administration (TGA) took a median of 391 days from application, which compares favourably with Europe at 478 days.[1] However, the US Food and Drug Administration (FDA) approves new drug applications faster than any other country at a median of 304 days. There is a paucity of published data in any jurisdiction on how any accelerated drug approval mechanism reduces the time frame for availability compared to traditional evaluation processes. The FDA aims to review a priority application within six months as opposed to 10 months under standard review.

The approval of new drugs is an increasingly complicated process. Clinical trial designs and procedures have become progressively more complex. Furthermore, the proliferation of biological therapies (including biosimilar medicines) compared to traditional small-molecule drugs has added layers of intricacy to the evaluation process. As such, a traditional drug regulatory framework may no longer be the most appropriate assessment process for dealing with quickly evolving scientific advances.

The traditional approach in the assessment of a new drug involves a sequence of clinical trials (phase I–III). Accumulated evidence of dose justification, efficacy and safety in specified treatment indications and target populations then enables the drug's sponsor to apply for registration of the drug. However, in the last 20 years, several regulatory bodies have tried to develop and test fast-track approval processes for drugs to treat severe diseases for which the options are limited.

Following a review[1] the TGA consulted about expedited approvals[2] and has introduced a priority review pathway. This aims to assess new drugs within 150 days.[3] The European Medicines Agency (EMA) introduced its PRIME (Priority Medicines) program of accelerated approval and priority review in 2016. The FDA already had such programs, and in 2017 new molecule drug approvals were at a 20-year record of 46 (more than double the 22 approved in 2016). Of the 46 new molecular entities, 18 (more than half for oncology indications) received approval through the fast-track pathway.[4]

In these programs drugs for serious illnesses are rapidly approved on the basis of limited clinical trial data or data reliant on surrogate outcome measures, some of which are biochemical, for example glycated haemoglobin (HbA1c), rather than clinical. Anticancer drugs may be approved on response rates, often measured over relatively short time frames, rather than on improved survival. Between 2009 and 2013, the EMA approved the use of 48 oncology drugs for 68 treatment indications, eight of which were approved on the basis of a single-arm trial.[5] An analysis of the data reports that in approximately half (35 of 68) of the indications there was a significant improvement in survival or quality of life, whereas in the other half, the benefit remained uncertain.

Advocates of rapid access to new therapies claim that targeted treatments such as modern immunotherapies do not fit current regulatory processes. With an enhanced contemporary understanding of disease pathogenesis pre-study, novel immuno-oncology drugs are clinically tested in trials with small patient numbers and often in the setting of knowing the patient's genetic profile. It is claimed that these attributes allow for better prediction of response with fewer significant adverse events. Furthermore, advances in digital technology, remote monitoring, patient sensors and data analytics are allowing for improved recording of reliable and validated patient-related outcomes in studies with smaller sample sizes.

Critics of faster access to new drugs are concerned that it comes at the expense of patient safety and increases the financial risks for the individual and society.[6] Moreover, the acceptance of overseas regulatory decisions to facilitate rapid drug approval in another country is frequently complicated by significantly different assessment criteria across the major jurisdictions. There are also distinctive differences in clinical practice, making the extrapolation of regulatory decisions to other countries potentially hazardous.[7]

Canadian (1998–2013) and US (2001–10) experience with expedited approval processes showed that fast-tracked drugs were twice as likely to be subsequently withdrawn

from the market or to receive major safety warnings compared to drugs approved by standard processes. Analysis of the FDA fast-track data found that it took a median of 4.2 years after a drug's initial approval for major safety concerns (including death) to come to light. Postmarketing problems were more common for psychiatric drugs and biological therapies.[8]

A challenge for drug regulators is that many new drugs granted accelerated consideration are often not the first in their class as nowadays several companies may work on the same drug targets (e.g. programmed death ligand therapies). In 2017, only one-third (15/46) of accelerated new drug approvals in the US were first-in-class therapies, compared with up to 50% in 2012.[4] In addition, many of the drugs spiking interest for rapid access are targeted immunotherapies that may have the potential to be used across multiple treatment indications, in the same way that rituximab can be used to treat various autoimmune diseases and cancers. Across the globe, many regulators have published guidelines on the eligibility criteria and processes for managing expedited drug approval, but there is a lack of clarity on the post-authorisation handling of safety and efficacy failures following accelerated approval.

In March 2018, the TGA announced a provisional approval pathway. This will allow drugs to be available for up to six years based on preliminary data.[9] The anticancer drug olaratumab is the first drug to be considered for provisional approval in Australia.

Access to new therapies is a balance between evidence (determining the risk of acceptable adverse effects versus efficacy) and the speed of availability, intersected by the issue of affordability. Making a drug available early with temporary authorisation is not a new concept, particularly for patients with life-threatening or seriously disabling conditions for which there is a clear unmet therapeutic need. Temporary access is akin to a learner driver receiving their provisional licence – a full licence is only granted after more experience. Rapidly approved drugs should receive provisional registration for a period of three years and the drug company should be required to provide annual data on the postmarketing experience.

In Australia at present, sponsor companies are required to report all negative outcomes that they become aware of, but there is no imperative for them to actively and meticulously seek out adverse events, or confirm efficacy after approval. As pharmacovigilance relies on spontaneous voluntary reporting of adverse effects by clinicians, it is highly likely that safety concerns are under-reported.

Improving the scientific rigor of postmarketing information to track effectiveness and safety outcomes, either through independently monitored registry studies as a condition of initial registration or data linkage (e.g. with linking of Pharmaceutical Benefits Scheme and Medicare Benefits Scheme datasets), will be of paramount importance during any provisional registration period. If efficacy outcomes in the real-world environment are not confirmed or a significant safety problem emerges, then the drug's registration should be suspended, at least for previously untreated patients, until the sponsor satisfactorily addresses the problems. <

Paul Kubler received sponsorship from Bristol-Myers Squibb to attend the 2017 EULAR Annual European Congress of Rheumatology and has acted as a consultant to Abbvie, Eli Lilly and Reckitt Benckhiser.

REFERENCES

1. Sansom L, Delaat W, Horvath J. Review of medicines and medical devices regulation: report on the regulatory framework for medicines and medical devices. Canberra: Department of Health; 2015. http://www.health.gov.au/internet/main/publishing.nsf/content/expert-review-of-medicines-and-medical-devices-regulation#report1 [cited 2018 Jul 1]
2. Therapeutic Goods Administration. Consultation: expedited pathways for prescription medicines. Eligibility criteria and designation process. Version 1.0, Oct 2016. Canberra: Therapeutic Goods Administration; 2016. https://www.tga.gov.au/consultation/consultation-expedited-pathways-prescription-medicines [cited 2018 Jul 1]
3. Therapeutic Goods Administration. Priority review registration process: for priority review designated prescription medicines. Version 1.1, July 2017. Canberra: Therapeutic Goods Administration; 2017. https://www.tga.gov.au/publication/priority-review-registration-process [cited 2018 Jul 1]
4. Center for Drug Evaluation and Research. Advancing health through innovation: 2017 new drug therapy approvals. Silver Spring (MD): US Food and Drug Administration; 2018. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm537040.htm [cited 2018 Jul 1]
5. Davis C, Naci H, Gurpinar E, Poplavska E, Pinto A, Aggarwal A. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. BMJ 2017;359:j4530. https://doi.org/10.1136/bmj.j4530
6. Ma CKK, Danta M, Day R, Ma DDF. Dealing with the spiralling price of medicines: issues and solutions. Int Med J 2018;48:16-24. https://doi.org/0.1111/imj.13652
7. Martin J, Shenfield G. The hazards of rapid approval of new drugs. Aust Prescr 2016;39:2-3. https://doi.org/10.18773/austprescr.2016.005
8. Lupkin S. Nearly 1 in 3 recent FDA drug approvals followed by major safety action. Scientific American 2017 May 9.
9. Therapeutic Goods Administration. Provisional approval pathway: prescription medicines. 2018 Mar 20. Canberra: TGA; 2018. www.tga.gov.au/provisional-approval-pathway-prescription-medicines [cited 2018 Jul 1]

LETTERS

Letters to the Editor

Electronic medication management

Aust Prescr 2018;41:100
https://doi.org/10.18773/austprescr.2018.036

We read the editorial by Robert Pearce and Ian Whyte with interest.[1] We agree that electronic medication management is a step forward in access to prescribing and administration records with capability for passive and active decision support.

Electronic medication systems have positively impacted the antimicrobial stewardship post-prescribing rounds conducted at our health service. At the click of a button, we get a snapshot of all current hospital inpatients prescribed an antimicrobial. This significantly improves efficiency. Also, electronic approval rates for restricted antimicrobials have increased significantly related to the embedded clinical-decision support that alerts prescribers when a restricted antimicrobial is being prescribed. We recognise, however, that this has not removed the need for a separate electronic approval system for antimicrobials, or antimicrobial stewardship post-prescribing rounds.

We acknowledge that the challenges of implementing electronic medication management include developing a clear process of local stakeholders having input and being able to provide timely feedback on local improvements to generic software. For antimicrobials, we have recommended changes on common dosing and turning on of some alerts that were initially turned off to minimise alert fatigue.

Electronic medication management also offers new opportunities to practise antimicrobial stewardship. It is easy and fast to identify patients on any antimicrobial, not just the restricted ones that have made it into the electronic antimicrobial approval system. This allows the scope of antimicrobial stewardship teams to potentially expand to review prescribing practice for non-restricted antimicrobials rather than traditionally relying on usage data.

Lyn-li Lim
Antimicrobial stewardship physician

Kylie D'Arcy-Evans
Antimicrobial stewardship pharmacist

Sonia Koning
Lead antimicrobial stewardship pharmacist

Eastern Health, Melbourne

REFERENCES

1. Pearce R, Whyte I. Electronic medication management: is it a silver bullet? Aust Prescr 2018;41:32-3. https://doi.org/10.18773/austprescr.2018.012

Ian Whyte, one of the author's of the article, comments:

This correspondence highlights the significant advantages of having rapid access to individual prescribing information. This is not only true in antimicrobial stewardship, but also for reviewing the use of high-risk drugs such as anticoagulants, for auditing venous thromboembolism prophylaxis and for medication reconciliation.

Electronic medication management should provide opportunities for other groups of clinicians to streamline their processes, as the antimicrobial stewardship group in Eastern Health has shown.

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.

Labels for prescription medicines

Aust Prescr 2018;41:101
https://doi.org/10.18773/austprescr.2018.037

Thank you for the article on safer dispensing labels.[1] A patient-centric label should have the generic name in bold and prominently printed and the brand name in less prominent print. This should improve patient recognition of medications, and avoid duplications of different brand names often dispensed by pharmacists.

Ashok Chotai
GP, Brisbane

REFERENCE

1. La Caze A. Safer dispensing labels for prescription medicines. Aust Prescr 2018;41:46-9. https://doi.org/10.18773/austprescr.2018.009

ARTICLE

Travelling with medicines in 2018

Nicholas Zwar
Dean, School of Medicine, University of Wollongong, NSW

Keywords
contraception, diabetes, diarrhoea, Pharmaceutical Benefits Scheme, travel

Aust Prescr 2018;41:102–4
https://doi.org/10.18773/austprescr.2018.034

SUMMARY

Planning ahead is key for travelling with medicines to ensure sufficient supplies, compliance with legal restrictions and adequate documentation.

In general, the Pharmaceutical Benefits Scheme allows up to a six-month supply of subsidised drugs to be taken overseas for personal use.

Medicines should be transported in their original packaging whenever possible. Refrigeration during flight is seldom necessary.

Some medicines, such as insulin, will require adjustment of dosing with a change of time zones.

Travellers should avoid purchasing medicines in low-income countries if possible. Substandard and counterfeit medicines are common.

Introduction

In 2016, Australian residents made 9.9 million short-term overseas departures.[1] As greater numbers of older people and those with chronic conditions are travelling, health professionals (in particular GPs and pharmacists) will be providing more advice on travelling with medicines. Carrying medicines while travelling is common. A US survey of over 13 000 travellers found 58% were taking daily medication.[2]

A review of medicines before travel may reduce the risk of medicine-related problems. Caution is needed if introducing potentially toxic medicines or those that require monitoring. Be cautious when prescribing hypnotics to assist with jet lag, especially in the elderly, as the drugs are associated with confusion and an increased risk of falls.

Before travel, advise patients on the medicines required specifically for travel such as antimalarials and vaccines. The US Centers for Disease Control and Prevention website and 'Yellow Book' publication provide information on travel risks and preventive advice.[3] Advise also on the risks of purchasing drugs overseas given the increasing problem of substandard and counterfeit medicines.

Supply of medicines for travel

Travellers need to take adequate supplies of their regular drugs and check that the medicines will not expire during the trip. However, there are legal restrictions on taking medicines subsidised by the Pharmaceutics Benefits Scheme (PBS) overseas. Only a reasonable quantity can be taken overseas for the personal use of the traveller or someone they are accompanying such as a child. Information for travellers is available on the Medicare Australia website or by phone.[4] In general, a supply for up to six months is not questioned, but up to 12 months may be permitted for some drugs such as antihypertensives. For authority items only six months is allowed. Prescriptions can be annotated with PBS Regulation 24 to allow the pharmacist to dispense the original and repeat supplies of pharmaceutical benefits at the same time.

The Office of Drug Control[5] recommends that Australians going overseas carry either a prescription or a doctor's letter stating that the traveller is under their treatment and that the drugs have been prescribed for the traveller's personal use. The doctor's letter must specify the name and dose of the drugs. Generic drug names are preferable as brand names vary from country to country.

Legal restrictions on travelling with medicines

Areas of substantial difficulty and uncertainty are the country-by-country legal restrictions for potentially addictive drugs such as opioids and psychotropic drugs including amphetamines. The International Narcotics Control Board (INCB), an independent and quasi-judicial body for implementation of the United Nations Drug Control Conventions, has issued guidelines for individuals travelling with narcotic and psychotropic drugs for personal use.[6] These recommendations state that up to a 30-day supply is allowable, providing the drugs have been legally prescribed in the country of origin. Medical marijuana is an emerging issue with current INCB guidelines stating that tetrahydrocannabinol is always prohibited.

A study has reviewed the requirements for travelling with medicines in 25 countries that were

either leading sources of migration to Australia (10 countries) or frequent destinations for Australian travellers (15 countries).[7] This study involved searching the embassy websites and emailing the embassy of each country. The information available and response from embassies was limited. In all the 25 countries studied, travellers could bring at least a 30-day supply of medicines that had been obtained by prescription and packaged in a pharmacy with appropriate labelling for identification. No countries were following the INCB recommendations for opioids and psychotropic drugs and in general, where information was available, the countries were implementing more restrictive measures.

Packing medicines for travel

Travellers should take their prescribed drugs in their original containers. To ensure that they are available when needed, carry medicines in hand luggage or divided between hand luggage and checked luggage. Some medicines are affected by temperature and this creates potential problems during travel, especially if refrigeration is required. In general, airlines are not prepared to take responsibility for storing medicines in aircraft refrigerators and, even if they are, there is a risk of the drugs getting lost. Insulin remains stable for several months at room temperature, so refrigeration during air travel is not necessary. The consumer medicine information for thyroxine recommends storage in a refrigerator at 2–8°C, but this is definitely not needed for short periods such as air travel.

Diabetes

Planning ahead is particularly important for travellers with diabetes.[8] Permission may be needed from the airline to take diabetes equipment (e.g. pen needles, insulin pump consumables, fingerprick devices and lancets) on board the aircraft. In general, all the documentation required by the airline is a doctor's letter.

The timing of doses is an issue when flying across multiple time zones. Patients can be advised to take their glucometer to monitor blood sugar and a supply of glucagon or a rapidly acting carbohydrate as a precaution against hypoglycaemia. People on oral hypoglycaemic drugs should take them as prescribed according to local time. Adjustment of insulin dosing is not usually needed for trips with a change of time zone of less than four hours. East or west trips with greater time zone changes may require adjustment and detailed advice from the GP or specialist depending on the person's insulin regimen. If this advice is difficult to access, the website Diabetes Travel provides a guide.[9] In flight, bolus or mealtime insulin should only be injected once the meal has been served as turbulence can delay food service.

Contraception

Travel across time zones can cause confusion about when to take the oral contraceptive pill. Regular dosing is especially important for the progestogen-only pill. The risk of decreased effectiveness arises with flying west as the time between doses is prolonged if based on the time at the destination. Travellers taking the oral contraceptive pill can take a second watch and leave this set to the time at home. When adapting to local time on arrival, the traveller should err on the side of a shorter dosage interval rather than extending the dosage interval. Other forms of hormonal contraception such as implants and the vaginal ring are not affected by time zone changes.

The extent to which the risk of travel-related deep vein thrombosis is increased by the combined contraceptive pill is uncertain. In the absence of other risk factors, women can be advised to use the standard precautions which include exercises and maintaining hydration. Compression stockings are an additional precaution. Aspirin has not been shown to be effective at preventing deep vein thrombosis. It is associated with an increased risk of gastrointestinal bleeding, so aspirin cannot be currently advised for prophylaxis.

Travellers' diarrhoea

Travellers' diarrhoea may interfere with absorption of the oral contraceptive pill. The general advice is to continue taking the oral contraceptive pill but use additional contraception for the duration of the illness and a further seven days. The absorption of other medicines such as lithium and digoxin may be affected by travellers' diarrhoea. People with renal disease and with diabetes should be particularly careful to maintain hydration during episodes of travellers' diarrhoea.[10]

Purchasing medicines overseas

Travellers need to be aware that drugs have different names in different countries and that some medicines may not be available. Buying medicines overseas, particularly in the developing world and via the internet,[11] is a risk given the prevalence of substandard and counterfeit medicines. In a review of studies from 25 different countries (predominantly low-income or lower middle-income countries) the median prevalence of substandard or counterfeit medicines was 28.5% (range 11–48%). Antimicrobials were the most frequently substandard group and Asia and Africa were the continents most affected by the problem. Fake or substandard antimalarials are a major problem.[12] The World Health Organization (WHO) has estimated that falsified drugs represent

up to 50% of drugs sold in some African countries. The WHO also estimates that drugs purchased over the internet from websites that conceal their physical address are counterfeit in over 50% of cases.

Clearly, travellers need to be advised to purchase their drugs, including antimalarials if needed, before leaving Australia. In the event that they do have to purchase antimalarial or other drugs overseas, they should try to buy from a reputable source and carefully examine the packaging. The traveller could telephone their travel insurance hotline for advice on services. The International Society of Travel Medicine has an online list of travel medicine clinics and contacting one of these would be another option for local advice about medicines.[13] If travellers do choose to buy medicines over the internet they can look for the Verified Internet Pharmacy Practice Sites (VIPPS) Seal of the National Association of Boards of Pharmacy.[14]

Medical kits for travel

These kits can be quite extensive depending on the nature of travel and include first aid items such as antiseptic and dressings, illness care items such as analgesics, antidiarrhoeals and rehydration salts, and preventive care items such as hand sanitiser, insect repellent, sunscreen and condoms. Commercially available kits have the advantage of having a list of contents and instructions as well as a document explaining that the items are being carried for personal use.

Conclusion

Planning and preparation are the key elements of travelling safely with medicines. <

Conflict of interest: none declared

REFERENCES

1. Australian Bureau of Statistics. 3401.0 - Overseas arrivals and departures, Australia, Dec 2016. 2017 Feb 13. www.abs.gov.au/ausstats/abs@.nsf/products/961B6B53B87C130ACA2574030010BD05 [cited 2018 Jul 1]
2. LaRocque RC, Rao SR, Lee J, Ansdell V, Yates JA, Schwartz BS, et al. Global TravEpiNet: a national consortium of clinics providing care to international travelers--analysis of demographic characteristics, travel destinations, and pretravel healthcare of high-risk US international travelers, 2009-2011. Clin Infect Dis 2012;54:455-62. https://doi.org/10.1093/cid/cir839
3. Centers for Disease Control and Prevention. Travelers' health. wwwnc.cdc.gov/travel [cited 2018 Jul 1]
4. Department of Human Services. Travelling overseas with PBS medicine. 2018 May 12. www.humanservices.gov.au/individuals/services/medicare/travelling-overseas-pbs-medicine [cited 2018 Jul 1]
5. Department of Health. The Office of Drug Control. www.odc.gov.au [cited 2018 Jul 1]
6. United Nations Office on Drugs and Crime, International Narcotics Control Board, World Health Organization. Guidelines for national regulations concerning travellers under treatment with internationally controlled drugs. Vienna: UNODC; 2012. www.incb.org/incb/en/publications/guidelines-for-use-by-competent-national-authorities.html [cited 2018 Jul 1]
7. Mutie M, Cooper G, Naunton M, Kyle, G, Zwar N. Travelling with medications and medical equipment across international borders. Travel Med Infect Dis 2014;12:505–10. https://doi.org/10.1016/j.tmaid.2014.07.007
8. Zwar N. Guide to travelling for people with diabetes: be prepared. Endocrinol Today 2016;5:6-9.
9. Kerr D, Martinez J. Diabetes Travel. Time zones. www.diabetestravel.org/time-zones [cited 2018 Jul 1]
10. Lea-Henry T, Baird-Gunning J, Pretzel E, Roberts D. Medication management on sick days. Aust Prescr 2017;40:186-73. https://doi.org/10.18773/austprescr.2017.057
11. Kelly B. Online pharmacies: buyer beware. Aust Prescr 2015;38:186-7. https://doi.org/10.18773/austprescr.2015.067
12. Almuzaini T, Choonara I, Sammons H. Substandard and counterfeit medicines: a systematic review of the literature. BMJ Open 2013;3:e002923. https://doi.org/10.1136/bmjopen-2013-002923
13. International Society of Travel Medicine. Global travel clinic directory. www.istm.org [cited 2018 Jul 1]
14. National Association of Boards of Pharmacy. VIPPS. 2018. www.nabp.pharmacy/programs/vipps [cited 2018 Jul 1]

FURTHER READING

INDRO e.V. Travel Guide Index [internet]. https://indro-online.de/en/methadone-worldwide-travel-guide [cited 2018 Jul 1]

Australian Prescriber
VOLUME 41 : NUMBER 4 : AUGUST 2018

ARTICLE

Infantile colic

SUMMARY

Infantile colic is a common, self-resolving condition. It has important adverse associations including maternal depression, child abuse and early cessation of breastfeeding.

There are many proposed causes of colic, however none is definitive. Colic is likely to be an exacerbation of normal infant crying brought about by physiological and psychosocial factors.

There is no known single effective treatment for colic. The mainstay of management is exclusion of organic causes, explanation of the natural history of colic, parental support, offering strategies to deal with the infant's feeding and sleep, and exploration of settling techniques.

The probiotic *Lactobacillus reuteri* DSM17938 may be trialled for exclusively breastfed infants with colic. Its efficacy in formula-fed babies is unknown.

An allergy to cow's milk protein accounts for a minority of cases. Hypoallergenic formula, and dietary exclusion for breastfeeding mothers, should only be tried in infants with other clinical features of cow's milk allergy.

Valerie Sung
Paediatrician, Centre for Community Child Health and Department of General Medicine, Royal Children's Hospital

Early career research fellow, Murdoch Children's Research Institute

Senior honorary fellow, University of Melbourne

Melbourne

Keywords
colic, breastfeeding, infant formula, probiotics

Aust Prescr 2018;41:105–10

https://doi.org/10.18773/austprescr.2018.033

Introduction

Infantile colic describes excessive crying of unknown cause in otherwise well infants. Colic affects up to 20% of infants,[1] and is one of the most common presentations to the primary health sector in early life. It resolves spontaneously after the first three to four months of life.

Colic is traditionally defined by the Wessel's criteria of crying or fussing more than three hours of the day for more than three days of the week.[2] The new Rome IV criteria define it as 'recurrent and prolonged periods of infant crying, fussing or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved'.[3] The diagnosis can be assumed after exclusion of potential organic causes.

Although colic is considered to be benign, it is a major burden to families, health professionals and the health system. Colic is strongly associated with maternal depression[4] and is the strongest risk factor for shaken baby syndrome.[5] It is also a common cause of early breastfeeding cessation.[6] Crying beyond the usual colicky period can be linked to later sleep problems, allergic disorders, family dysfunction, and behavioural problems.[7,8]

Causes of colic

Despite years of research, the aetiology of colic remains elusive and there are many proposed theories. Does colic represent the most severe spectrum of normal infant distress, or is it a manifestation of underlying gastrointestinal, neurological or psychosocial disorders? Perhaps infant colic can be best regarded as an exacerbation of normal infant behaviour by a mixture of physiological and psychosocial factors.[9]

Colic should only be diagnosed after exclusion of organic causes. These occur in less than 10% of infants presenting with crying.[10,11] Most organic causes present with other associated features (Table 1).

Is it a gastrointestinal disorder?

The word 'colic' implies an abdominal origin. Postulated gastrointestinal mechanisms have included increased intraluminal gas, gut dysmotility, and visceral pain, but none is proven.[12,13] Recent research has focused on the role of gut microbiota, with more than a dozen case-control studies suggesting that infants with colic may have differences in gut microbiota compared to those without colic.[14,15] The majority of studies have found that Gram-negative organisms such as *Escherichia* species occur more frequently in colicky infants than in controls. Other studies have found fewer *Lactobacillus* species in those with colic.[14,15] In addition, some studies have suggested that infants with colic have increased gut and systemic inflammatory markers when compared to those without colic.[16] However, the pathophysiological evidence for the role of gut microbiota and inflammation is still far from conclusive.[17]

Gastro-oesophageal reflux

Gastro-oesophageal reflux has been regarded as having a role in irritable infants, however anti-reflux medicines are ineffective in reducing crying.[18,19] Studies have failed to show any correlation between

Table 1 **Organic causes to exclude in a crying infant**

Conditions to exclude	Additional clinical features
Cow's milk protein allergy	Significant vomiting Feeding difficulties Diarrhoea with mucus or blood Poor weight gain Extensive eczema First-degree family history of atopy
Gastro-oesophageal reflux disease	Frequent significant vomiting (>5 times per day) Haematemesis Feeding difficulties Poor weight gain
Lactose intolerance or overload	Watery, frothy, explosive diarrhoea AND perianal excoriation or ulcerations
Inguinal hernia	Vomiting Lump in inguinal region
Intussusception	Acute onset of vomiting, pallor, irritability Abdominal mass, rectal bleeding
Infection: urinary tract infection, meningitis, otitis media	Fever Lethargy Poor feeding, poor weight gain Perinatal risk factors for sepsis
Hydrocephalus	Increasing head circumference/macrocephaly Vomiting Lethargy
Hair tourniquet	Hair tourniquet around fingers or toes
Foreign body in eye	Acute distress, history of foreign body penetration in eye
Non-accidental injury	Bruising or petechiae Other features of physical injury

pathological gastro-oesophageal reflux and crying in infants less than three months old.[20] In the absence of frequent vomiting, haematemesis and poor weight gain, gastro-oesophageal reflux disease is an unlikely cause of infant crying.[21]

Cow's milk protein allergy

An allergy to cow's milk protein has been implicated as a cause of irritability,[22,23] but accounts for probably less than 5% of cases of colic.[24] It should be considered if the crying infant has feeding difficulties (during the day as well as at night), failure to thrive, significant vomiting, diarrhoea with mucus or blood, widespread eczema and a first-degree family history of atopy. The diagnosis can be confirmed if the symptoms resolve after excluding dairy food from the diet of breastfeeding mothers or using hypoallergenic formula (usually for a two-week trial period), together with reproduction of the symptoms on re-challenge with cow's milk protein.

Lactose intolerance and overload

Evidence for the role of lactose intolerance or overload in colic is mixed and inconclusive.[22,25-28] Lactose intolerance may be secondary to an underlying pathology such as cow's milk protein allergy or gastroenteritis. Lactose overload is usually a result of excessively frequent breastfeeding whereby the baby is snacking on the foremilk which has a high lactose content. Lactose intolerance or overload should be considered in the presence of watery, frothy, explosive diarrhoea with significant perianal excoriation or ulceration (due to acidic stools).

Possible neurological or psychosocial causes

Evidence for a neurological basis for colic is limited,[29] although recent studies have suggested colic may be associated with both childhood migraine later on in life and migraines in the mother.[30-32] Psychosocial factors such as infant temperament, mother–infant

interactions, maternal anxiety and depression may be important contributors to colic.[33,34] Maternal smoking may be a risk factor.[35,36]

Management options

Despite years of research, effective management options for colic are limited. Table 2 summarises the different proposed management options and the evidence for their effectiveness.

Drug therapies

Anticholinergic drugs, such as dicyclomine and cimetropium, reduce crying,[37-40] but have potentially dangerous adverse effects, including drowsiness, apnoeas and coma.[41] They are not recommended for infants younger than six months old. Despite its widespread use for colic, simethicone, an anti-foaming agent to reduce intraluminal gas, is not effective.[37-40,42] Proton pump inhibitors are conclusively ineffective.[18,19] Considering that there is increasing evidence of their association with adverse effects such as an increased risk of infections,[43] they should not be routinely used for managing colic. There have been no studies examining the effect of gripe water on colic.

Non-drug therapies

Many natural remedies have been tried, but not rigorously studied. Few have evidence of effectiveness.

Probiotics

Recent evidence has emerged of a possible role for probiotics in infant colic. These are 'live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host'.[44] *Lactobacillus reuteri* DSM17938 reduced infant crying in four double-blind randomised trials, two open-label and one single-blinded trial of exclusively breastfed infants with colic, at a dose of 1 x 10^8 colony-forming units per day. These studies all had sample sizes under 80.[45-51] In contrast, an Australian double-blind randomised trial, the largest to date (n=167), including both breastfed and formula-fed infants with colic, concluded that *L. reuteri* was ineffective.[52] The negative findings were replicated in a more recent smaller double-blind trial of 20 breastfed infants with colic.[53]

In response to the conflicting results, a meta-analysis pooled raw data from four of the higher quality double-blind trials, involving 345 infants with colic (174 probiotic, 171 placebo).[54] The reduction in daily crying from baseline to 21 days in the probiotic group was 25 minutes more than in the placebo group (adjusted mean difference in change from baseline -25.4, 95% confidence interval (CI) -47.3, -3.5). The probiotic group was more likely to experience treatment success (adjusted incidence ratio 1.7, 95% CI 1.4, 2.2). Intervention effects were more pronounced in breastfed infants (number needed to treat 2.6, 95% CI 2.0, 3.6). The meta-analysis of individual participant data concluded that *L. reuteri* DSM17938 was effective in exclusively breastfed infants with colic. There was insufficient evidence to make conclusions for formula-fed infants with colic.[54]

Table 2 **Summary of evidence from randomised controlled trials for the management of colic**

Effectiveness	Intervention
Effective for exclusively breastfed infants with colic	Probiotic *Lactobacillus reuteri* DSM17938
Possibly effective	Hydrolysed formula
	Hypoallergenic diet in breastfeeding mothers
	Reduced stimulation
	Improved parental responsiveness
	Focused parent counselling
	Acupuncture
Ineffective	Simethicone
	Spinal manipulation
	Lactase
	Soy formula
	Fibre-enriched formula
	Carbohydrate alteration
	Increased carrying
	Car ride simulator
	Crib vibrator
Effective but possibly harmful	Dicyclomine, cimetropium
	Herbal mixtures
	Swaddling
Effective but short-lived effects	Sucrose

Other non-drug therapies

Next to *L. reuteri*, the best evidence for colic management is the use of hypoallergenic formulae or eliminating dairy foods from the diet of breastfeeding mothers. However, not all unsettled infants respond and most studies examining maternal elimination diets have methodological limitations.[37-40,55,56] These approaches are probably only effective for babies who have an underlying allergy to cow's milk protein.[56]

Behavioural therapies such as reducing stimulation, improving parental responsiveness and parental counselling can be effective. However, the evidence comes from unblinded studies which are prone to bias.[37-40]

Acupuncture has been suggested to be effective in two recent studies, however there were methodological limitations in both.[57,58] Herbal mixtures given to infants with colic may be effective,[59-62]

however the consumption of large quantities of herbal teas has the potential to reduce milk intake and put infants at risk of nutritional deficiencies.[39] Swaddling the baby may be effective, however there is concern that it can increase the risk of hip dysplasia.[63,64]

Sucrose is effective in reducing crying but its effects are short-lived.[37-40] The use of lactase, soy or fibre-enriched formulae, massage, music and spinal manipulation have all been shown to be ineffective for colic.[37-40,65]

Recommendations

The first step for managing colic is to exclude organic causes of crying by careful history and examination. Infants who have significant feeding difficulties and frequent vomiting, especially those who are struggling to gain weight, have a strong family history of allergy, and those with increasing irritability beyond three months should be considered for a limited trial of a hypoallergenic diet. Hypoallergenic formula or dietary elimination should only be continued if symptoms resolve and then reappear after a re-challenge with cow's milk protein.

It is important to explore the family's perceptions of their infant's crying, listen to their worries, acknowledge their feelings of anger, frustration and exhaustion, and avoid being dismissive of their concerns. Discussing the different hypotheses surrounding colic, and addressing each hypothesis in relation to the individual infant and family, can be helpful.

It is essential to screen for maternal postnatal depression and also pay attention to paternal well-being. Clinicians should explore parental coping mechanisms during times of extreme crying, explain the neurological consequences of shaken baby syndrome and suggest strategies to prevent it. All families should be offered support and help around the infant's feeding, settling, and sleep. Feeding difficulties must be addressed and managed. Strategies to soothe the infant should be explored, with recommendations to reduce environmental stimuli.

Families can often be reassured by understanding the self-resolving nature of colic, offering at least one review and more where necessary, putting in place strategies to increase emotional and social supports, and acknowledging that it may be difficult, if not impossible, to 'teach' their infant to 'self-soothe' during the first few months of life. Most of all, it is vital to recognise that the family is usually doing the best they can for their baby, to allay any feelings of failure or guilt, and to encourage them to take adequate breaks from their crying infant.

If the infant is exclusively breastfed, a three-week trial of the probiotic *L. reuteri* DSM17938 can be considered. It is important to discuss that even though the probiotic has been shown to be effective in breastfed babies in most trials across the world, it has not been shown to be effective in Australia and cannot be recommended for formula-fed infants. In addition, although the probiotic is considered safe without short-term adverse effects, its longer term effects are unknown.

Conclusion

The mainstay of management for colic is to help families cope with their infant's symptoms, reduce the risks of parental depression, child abuse and early breastfeeding cessation, and to prevent the possibility of long-term adverse effects. The myths surrounding colic should be explored, and the lack of evidence for any one effective intervention should be explained. All families must be offered strategies to manage their infant's feeding, settling and sleep, together with a recommendation to reduce environmental stimuli. Although evidence for these strategies is limited, they are not harmful or expensive. Other management strategies should be considered on a case-by-case basis suited to each individual family. <

Valerie Sung reports personal fees from Mead Johnson Nutrition for contributions to education materials.

REFERENCES

1. Lucassen PL, Assendelft WJ, van Eijk JT, Gubbels JW, Douwes AC, van Geldrop WJ. Systematic review of the occurrence of infantile colic in the community. Arch Dis Child 2001;84:398-403. https://doi.org/10.1136/adc.84.5.398
2. Wessel MA, Cobb JC, Jackson EB, Harris Gs Jr, Detwiler AC. Paroxysmal fussing in infancy, sometimes called 'colic'. Pediatrics 1954;14:421-34.
3. Zeevenhooven J, Koppen IJN, Benninga MA. The new Rome IV criteria for functional gastrointestinal disorders in infants and toddlers. Pediatr Gastroenterol Hepatol Nutr 2017;20:1-13. https://doi.org/10.5223/pghn.2017.20.1.1
4. Vik T, Grote V, Escribano J, Socha J, Verduci E, Fritsch M, et al. Infantile colic, prolonged crying and maternal postnatal depression. Acta Paediatr 2009;98:1344-8. https://doi.org/10.1111/j.1651-2227.2009.01317.x
5. Barr RG. Preventing abusive head trauma resulting from a failure of normal interaction between infants and their caregivers. Proc Natl Acad Sci USA 2012;109 Suppl 2:17294-301. https://doi.org/10.1073/pnas.1121267109
6. Howard CR, Lanphear N, Lanphear BP, Eberly S, Lawrence RA. Parental responses to infant crying and colic: the effect on breastfeeding duration. Breastfeed Med 2006;1:146-55. https://doi.org/10.1089/bfm.2006.1.146
7. Savino F, Castagno E, Bretto R, Brondello C, Palumeri E, Oggero R. A prospective 10-year study on children who had severe infantile colic. Acta Paediatr Suppl 2005;94:129-32. https://doi.org/10.1111/j.1651-2227.2005.tb02169.x
8. Hemmi MH, Wolke D, Schneider S. Associations between problems with crying, sleeping and/or feeding in infancy and long-term behavioural outcomes in childhood: a meta-analysis. Arch Dis Child 2011;96:622-9. https://doi.org/10.1136/adc.2010.191312

9. Barr RG. Colic and crying syndromes in infants. Pediatrics 1998;102(Suppl E):1282-6.
10. Gormally S, Barr R. Of clinical pies and clinical clues: proposal for a clinical approach to complaints of early crying and colic. Ambul Child Health 1997;3:137-53.
11. Freedman SB, Al-Harthy N, Thull-Freedman J. The crying infant: diagnostic testing and frequency of serious underlying disease. Pediatrics 2009;123:841-8. https://doi.org/10.1542/peds.2008-0113
12. Gupta SK. Is colic a gastrointestinal disorder? Curr Opin Pediatr 2002;14:588-92.
13. Geertsma MA, Hyams JS. Colic--a pain syndrome of infancy? Pediatr Clin North Am 1989;36:905-19. https://doi.org/10.1016/S0031-3955(16)36728-1
14. Sung V, Cabana MD. Probiotics for colic: is the gut responsible for infant crying after all? J Pediatr 2017;191:6-8. https://doi.org/10.1016/j.jpeds.2017.09.010
15. Sung V, Pärtty A. Chapter 12 The association between intestinal microbiota and infant crying and behaviour. In: Browne PD, Claassen E, Cabana MD, editors. Microbiota in health and disease: from pregnancy to childhood. Wageningen, The Netherlands: Wageningen Academic Publishers; 2016. p. 219-43.
16. Pärtty A, Kalliomaki M, Salminen S, Isolauri E. Infantile colic is associated with low-grade systemic inflammation. J Pediatr Gastroenterol Nutr 2017;64:691-5. https://doi.org/10.1097/MPG.0000000000001340
17. de Weerth C, Fuentes S, de Vos WM. Crying in infants: on the possible role of intestinal microbiota in the development of colic. Gut Microbes 2013;4:416-21. https://doi.org/10.4161/gmic.26041
18. van der Pol RJ, Smits MJ, van Wijk MP, Omari TI, Tabbers MM, Benninga MA. Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. Pediatrics 2011;127:925-35. https://doi.org/10.1542/peds.2010-2719
19. Gieruszczak-Bialek D, Konarska Z, Skorka A, Vandenplas Y, Szajewska H. No effect of proton pump inhibitors on crying and irritability in infants: systematic review of randomized controlled trials. J Pediatr 2015;166:767-70.e3. https://doi.org/10.1016/j.jpeds.2014.11.030
20. Heine RG, Jaquiery A, Lubitz L, Cameron DJ, Catto-Smith AG. Role of gastro-oesophageal reflux in infant irritability. Arch Dis Child 1995;73:121-5. https://doi.org/10.1136/adc.73.2.121
21. Heine RG, Jordan B, Lubitz L, Meehan M, Catto-Smith AG. Clinical predictors of pathological gastro-oesophageal reflux in infants with persistent distress. J Paediatr Child Health 2006;42:134-9. https://doi.org/10.1111/j.1440-1754.2006.00812.x
22. Heine RG. Cow's-milk allergy and lactose malabsorption in infants with colic. J Pediatr Gastroenterol Nutr 2013;57:S25-S27. https://doi.org/10.1097/01.mpg.0000441930.13307.9b
23. Treem WR. Assessing crying complaints: the interaction with gastroesophageal reflux and cow's milk protein intolerance. In: Barr RG, St James-Roberts I, Keefe M, editors. New evidence on unexplained early infant crying: its origins, nature and management. Skillman, New Jersey: Johnson & Johnson Pediatric Institute; 2001. p. 165-76.
24. Barr R, Geertsma M. Colic: the pain perplex. In: Schechter N, Berde C, Yaster M, editors. Pain in infants, children and adolescents. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2003. p. 751-64.
25. Stahlberg MR, Savilahti E. Infantile colic and feeding. Arch Dis Child 1986;61:1232-3. http://dx.doi.org/10.1136/adc.61.12.1232
26. Miller JJ, McVeagh P, Fleet GH, Petocz P, Brand JC. Effect of yeast lactase enzyme on 'colic' in infants fed human milk. J Pediatr 1990;117:261-3. https://doi.org/10.1016/S0022-3476(05)80542-6
27. Kanabar D, Randhawa M, Clayton P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. J Hum Nutr Diet 2001;14:359-63. https://doi.org/10.1046/j.1365-277X.2001.00304.x
28. Kearney PJ, Malone AJ, Hayes T, Cole M, Hyland M. A trial of lactase in the management of infant colic. J Hum Nutr Diet 1998;11:281-5. https://doi.org/10.1046/j.1365-277X.1998.00108.x
29. Kirjavainen J, Jahnukainen T, Huhtala V, Lehtonen L, Kirjavainen T, Korvenranta H, et al. The balance of the autonomic nervous system is normal in colicky infants. Acta Paediatr 2001;90:250-4. https://doi.org/10.1111/j.1651-2227.2001.tb00299.x
30. Romanello S, Spiri D, Marcuzzi E, Zanin A, Boizeau P, Riviere S, et al. Association between childhood migraine and history of infantile colic. JAMA 2013;309:1607-12. https://doi.org/10.1001/jama.2013.747
31. Qubty W, Gelfand AA. The link between infantile colic and migraine. Curr Pain Headache Rep 2016;20:31. https://doi.org/10.1007/s11916-016-0558-8
32. Gelfand AA, Goadsby PJ, Allen IE. The relationship between migraine and infant colic: a systematic review and meta-analysis. Cephalalgia 2015;35:63-72. https://doi.org/10.1177/0333102414534326
33. Hiscock H, Jordan B. Problem crying in infancy. Med J Aust 2004;181:507-12.
34. Raiha H, Lehtonen L, Huhtala V, Saleva K, Korvenranta H. Excessively crying infant in the family: mother-infant, father-infant and mother-father interaction. Child Care Health Dev 2002;28:419-29. https://doi.org/10.1046/j.1365-2214.2002.00292.x
35. Canivet CA, Ostergren PO, Jakobsson IL, Dejin-Karlsson E, Hagander BM. Infantile colic, maternal smoking and infant feeding at 5 weeks of age. Scand J Public Health 2008;36:284-91. https://doi.org/10.1177/1403494807086981
36. Shenassa ED, Brown MJ. Maternal smoking and infantile gastrointestinal dysregulation: the case of colic. Pediatrics 2004;114:e497-505. https://doi.org/10.1542/peds.2004-1036
37. Hall B, Chesters J, Robinson A. Infantile colic: a systematic review of medical and conventional therapies. J Paediatr Child Health 2012;48:128-37. https://doi.org/10.1111/j.1440-1754.2011.02061.x
38. Cohen-Silver J, Ratnapalan S. Management of infantile colic: a review. Clinical Pediatrics 2009;48:14-7. https://doi.org/10.1177/0009922808323116
39. Garrison MM, Christakis DA. A systematic review of treatments for infant colic. Pediatrics 2000;106:184-90.
40. Lucassen PLBJ, Assendelft WJJ, Gubbels JW, van Eijk JTM, van Geldrop WJ, Neven AK. Effectiveness of treatments for infantile colic: systematic review. BMJ 1998;316:1563-9. https://doi.org/10.1136/bmj.316.7144.1563
41. Williams J, Watkins-Jones R. Dicyclomine: worrying symptoms associated with its use in some small babies. Br Med J (Clin Res Ed) 1984;288:901. https://doi.org/10.1136/bmj.288.6421.901
42. Metcalf TJ, Irons TG, Sher LD, Young PC. Simethicone in the treatment of infant colic: a randomized, placebo-controlled, multicenter trial. Pediatrics 1994;94:29-34.
43. Canani RB, Cirillo P, Roggero P, Romano C, Malamisura B, Terrin G, et al. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics 2006;117:e817-20. https://doi.org/10.1542/peds.2005-1655
44. Probiotics in food: health and nutritional properties and guidelines for evaluation. FAO Food and Nutrition Paper 85. Rome: Food and Agriculture Organization of the United Nations and World Health Organization; 2006. http://www.fao.org/publications/card/en/c/7c102d95-2fd5-5b22-8faf-f0b2e68dfbb6 [cited 2018 Jul 1]
45. Chau K, Lau E, Greenberg S, Jacobson S, Yazdani-Brojeni P, Verma N, et al. Probiotics for infantile colic: a randomized, double-blind, placebo-controlled trial investigating *Lactobacillus reuteri* DSM 17938. J Pediatr 2015;166:74-8. https://doi.org/10.1016/j.jpeds.2014.09.020
46. Savino F, Cordisco L, Tarasco V, Palumeri E, Calabrese R, Oggero R, et al. *Lactobacillus reuteri* DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. Pediatrics 2010;126:e526-33. https://doi.org/10.1542/peds.2010-0433
47. Savino F, Pelle E, Palumeri E, Oggero R, Miniero R. *Lactobacillus reuteri* (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study. Pediatrics 2007;119:e124-30. https://doi.org/10.1542/peds.2006-1222
48. Szajewska H, Gyrczuk E, Horvath A. *Lactobacillus reuteri* DSM 17938 for the management of infantile colic in breastfed infants: a randomized, double-blind, placebo-controlled trial. J Pediatr 2013;162:257-62. https://doi.org/10.1016/j.jpeds.2012.08.004
49. Mi GL, Zhao L, Qiao DD, Kang WQ, Tang MQ, Xu JK. Effectiveness of *Lactobacillus reuteri* in infantile colic and colicky induced maternal depression: a prospective single blind randomized trial. Antonie Van Leeuwenhoek 2015;107:1547-53. https://doi.org/10.1007/s10482-015-0448-9

50. Savino F, Garro M, Montanari P, Galliano I, Bergallo M. Crying time and RORg/FOXP3 expression in *Lactobacillus reuteri* DSM17938-treated infants with colic: a randomized trial. J Pediatr 2018;192:171-7.e1. https://doi.org/10.1016/j.jpeds.2017.08.062
51. Ashraf MW, Ayaz SB, Ashraf MN, Matee S, Shoaib M. Probiotics are effective in alleviating infantile colic: results of a randomized controlled trial held at Benazir Bhutto Hospital, Rawalpindi, Pakistan. Rawal Med J 2015;40:277-80. https://www.rmj.org.pk/?mno=177300 [cited 2018 Jul 1]
52. Sung V, Hiscock H, Tang M, Mensah FK, Nation ML, Satzke C, et al. Treating infant colic with the probiotic *Lactobacillus reuteri*: double-blind, placebo-controlled randomised trial. BMJ 2014;34:g2107. https://doi.org/10.1136/bmj.g2107
53. Fatheree NY, Liu Y, Taylor CM, Hoang TK, Cai C, Rahbar MH, et al. *Lactobacillus reuteri* for infants with colic: a double-blind, placebo-controlled, randomized clinical trial. J Pediatr 2017;191:170-8.e2. https://doi.org/10.1016/j.jpeds.2017.07.036
54. Sung V, D'Amico F, Cabana M, Chau K, Koren G, Savino F, et al. *Lactobacillus reuteri* to treat infant colic: a meta-analysis. Pediatrics 2018;141:e20171811. https://doi.org/10.1542/peds.2017-1811
55. Iacovou M, Ralston RA, Muir J, Walker KZ, Truby H. Dietary management of infantile colic: a systematic review. Matern Child Health J 2012;16:1319-31. https://doi.org/10.1007/s10995-011-0842-5
56. Nocerino R, Pezzella V, Cosenza L, Amoroso A, Di Scala C, Amato F, et al. The controversial role of food allergy in infantile colic: evidence and clinical management. Nutrients 2015;7:2015-25. https://dx.doi.org/10.3390/nu7032015
57. Landgren K, Kvorning N, Hallstrom I. Acupuncture reduces crying in infants with infantile colic: a randomised, controlled, blind clinical study. Acupuncture Med 2010;28:174-9. https://dx.doi.org/10.1136/aim.2010.002394
58. Reinthal M, Andersson S, Gustafsson M, Plos K, Lund I, Lundeberg T, et al. Effects of minimal acupuncture in children with infantile colic: a prospective, quasi-randomised single blind controlled trial. Acupunct Med 2008;26:171-82. http://dx.doi.org/10.1136/aim.26.3.171
59. Martinelli M, Ummarino D, Giugliano FP, Sciorio E, Tortora C, Bruzzese D, et al. Efficacy of a standardized extract of *Matricariae chamomilla* L., *Melissa officinalis* L. and tyndallized *Lactobacillus acidophilus* (HA122) in infantile colic: an open randomized controlled trial. Neurogastroenterol Motil 2017;29. Epub 2017 Jun 30. https://doi.org/10.1111/nmo.13145
60. Savino F, Cresi F, Castagno E, Silvestro L, Oggero R. A randomized double-blind placebo-controlled trial of a standardized extract of *Matricariae recutita*, *Foeniculum vulgare* and *Melissa officinalis* (ColiMil) in the treatment of breastfed colicky infants. Phytother Res 2005;19:335-40. https://doi.org/10.1002/ptr.1668
61. Alexandrovich I, Rakovitskaya O, Kolmo E, Sidorova T, Shushunov S. The effect of fennel (*Foeniculum vulgare*) seed oil emulsion in infantile colic: a randomized, placebo-controlled study. Altern Ther Health Med 2003;9:58-61.
62. Weizman Z, Alkrinawi S, Goldfarb D, Bitran C. Efficacy of herbal tea preparation in infantile colic. J Pediatr 1993;122:650-2. https://doi.org/10.1016/S0022-3476(05)83557-7
63. van Sleuwen BE, Engelberts AC, Boere-Boonekamp MM, Kuis W, Schulpen TW, L'Hoir MP. Swaddling: a systematic review. Pediatrics 2007;120:e1097-106. https://doi.org/10.1542/peds.2006-2083
64. Clarke N. Swaddling and hip dysplasia: an orthopaedic perspective. Arch Dis Child 2014;99:5-6. https://doi.org/10.1136/archdischild-2013-304143
65. Dobson D, Lucassen PL, Miller JJ, Vlieger AM, Prescott P, Lewith G. Manipulative therapies for infantile colic. Cochrane Database Syst Rev 2012:CD004796. https://doi.org/10.1002/14651858.CD004796.pub2

Australian Prescriber
VOLUME 41 : NUMBER 4 : AUGUST 2018

ARTICLE

Combining anticoagulation and antiplatelet drugs in coronary artery disease

SUMMARY

Most patients with stable coronary disease are managed with a single antiplatelet drug. For those who require anticoagulation, an antiplatelet drug may not be required.

Antiplatelet therapy for patients who have an acute coronary syndrome helps to prevent future cardiovascular events. This benefit can be increased by using two antiplatelet drugs.

The choice of drug is determined for each individual patient. Factors to consider include whether the patient had a stent inserted, the risk of bleeding and whether they have another indication for anticoagulation.

For patients without a stent, aspirin can be combined with a $P2Y_{12}$ antagonist for up to 12 months. Only one antiplatelet drug is recommended if the patient also needs long-term anticoagulation.

Following stent insertion, patients with an indication for anticoagulation have been treated with two antiplatelet drugs and an anticoagulant. Recent research suggests that selected patients may be managed with one antiplatelet drug and an anticoagulant. After 12 months it may be possible to manage the patients with an anticoagulant alone.

Jyotsna Janardan
General physician

Harry Gibbs
Program director, Outpatients, and Deputy director, General Medicine

Alfred Health, Melbourne

Keywords
acute coronary syndrome, anticoagulants, antiplatelets, coronary artery disease

Aust Prescr 2018;41:111–5
https://doi.org/10.18773/austprescr.2018.039

Introduction

Antiplatelet drugs play an important role in the secondary prevention of atherosclerotic coronary disease. They reduce the relative risk of subsequent vascular events (non-fatal myocardial infarction, non-fatal stroke and vascular death) by approximately 20%.[1] In patients with acute coronary syndromes, with or without percutaneous intervention, adding a second antiplatelet drug further reduces ischaemic events, albeit with a small increased risk of bleeding.[2] Often aspirin is used in combination with an antagonist of the $P2Y_{12}$ receptor, such as clopidogrel (see Fig. 1).

A significant proportion of patients with coronary artery disease have other conditions that require oral anticoagulants. These include atrial fibrillation, left ventricular thrombus or aneurysm, prosthetic heart valve, and venous thromboembolism. While there is evidence that oral anticoagulants reduce ischaemic events in patients with coronary artery disease, they are not used as sole therapy in patients with acute coronary syndromes. Following percutaneous coronary interventions, antiplatelet drugs are required to prevent in-stent thrombosis. In-stent thrombosis has a mortality of 50–70%,[3] so the use of one or two antiplatelet drugs together with an anticoagulant is often required. However, such combinations increase the risk of bleeding. Overall, treatment must be individualised with a careful assessment of the risks of thrombosis and bleeding to find the optimal balance between harm and benefit.

Risk assessment

There are a number of scoring systems that predict the risk of further coronary events after acute coronary syndrome, including the GRACE and TIMI scores.[4] There are also scoring systems that predict stroke in patients with atrial fibrillation, the commonest of which is the CHA_2DS_2Vasc score (Table 1).[5]

The assessment of bleeding risk is more difficult. The HAS-BLED score[5] (Table 2) is a commonly used bleeding risk score which includes risk factors for bleeding during warfarin therapy. It is not validated for patients receiving other oral anticoagulants. The HAS-BLED score's greatest use is in identifying modifiable risk factors for bleeding that may be improved, rather than identifying patients who should not be anticoagulated. Additional scores are in development – the GARFIELD-AF score[6] gives one-year rates of death, stroke and bleeding in atrial fibrillation and, while very promising, it does require further validation.

Anticoagulation in acute coronary syndrome without percutaneous coronary intervention

After an acute coronary syndrome, patients remain at risk for recurrent cardiovascular events despite standard medical therapy. This risk may be related

Fig. 1 **Treatment pathways after acute coronary syndrome**

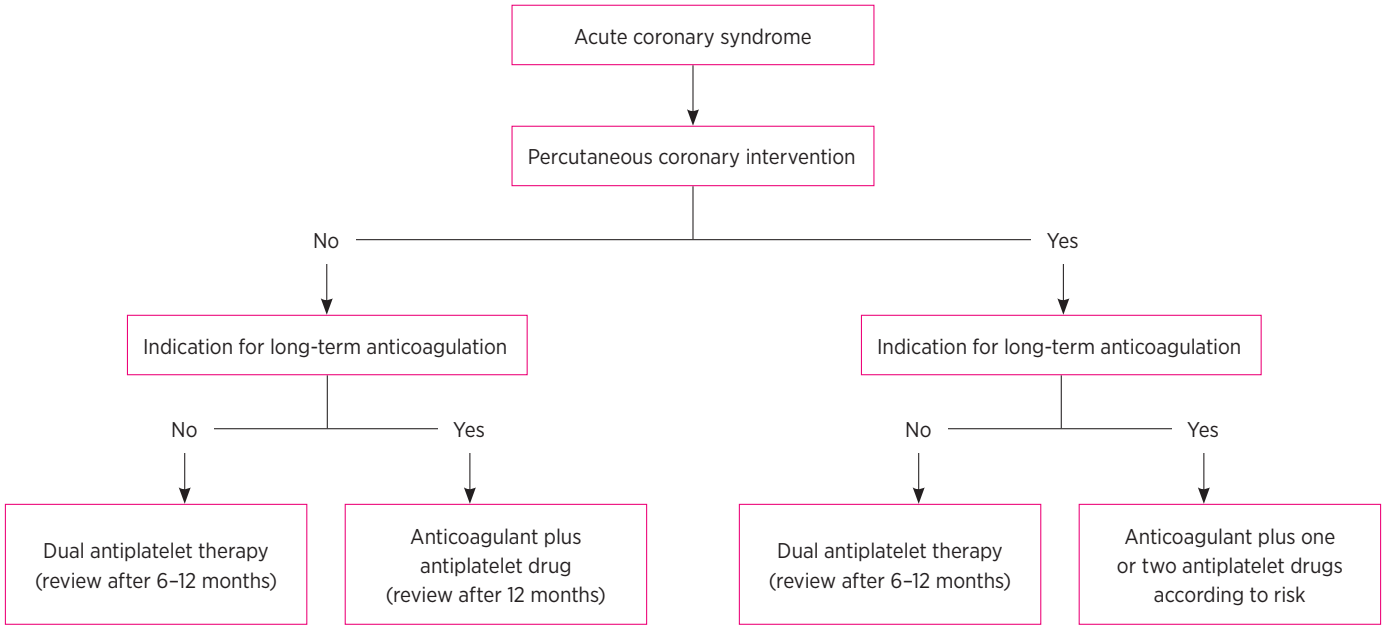


Table 1 **CHA_2DS_2Vasc score**

Criteria	Score (maximum 9)
Congestive heart failure	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/transient ischaemic attack/thromboembolism	2
Vascular disease (previous myocardial infarction, peripheral artery disease or aortic plaque)	1
Age 65–74 years	1
Sex female	1

Total score calculates risk of stroke
0 = low risk 1 = moderate risk >1 = high risk

Table 2 **HAS-BLED score**

Criteria	Score
Hypertension (systolic blood pressure >160 mmHg)	1
Abnormal liver or renal function (1 point each)	1
Stroke	1
Bleeding history	1
Labile INRs	1
Elderly (age >65 years)	1
Drugs/alcohol that promote bleeding (1 point each)	1

A score of 3 or more indicates an increased one-year bleed risk on anticoagulation sufficient to justify caution or more regular review.

to an excess of thrombin production that persists beyond the acute presentation.[7] All patients require antiplatelet drugs, but the regimen is influenced by any need for anticoagulation.

Patients without a pre-existing indication for anticoagulation

The results of several studies indicate that therapeutic anticoagulation using oral anticoagulants is not routinely recommended for patients with acute coronary syndromes who do not have another indication for anticoagulant therapy.

Multiple randomised studies have assessed the outcomes of warfarin and aspirin versus aspirin alone in acute coronary syndromes. A meta-analysis of 25 307 patients showed that in studies of warfarin with a target INR of 2–3, the addition of aspirin was associated with a significant reduction of major adverse events (all-cause death, non-fatal myocardial infarction, and non-fatal thromboembolic stroke) but with an increased risk of major bleeding.[8] When all trials, irrespective of INR control, were included there was no reduction in cardiac events, but there was a significant increase in major bleeding. Widespread use

of long-term warfarin in these patients is therefore not recommended.

More recent trials have studied a possible role for the newer oral anticoagulants. Rivaroxaban[9] and apixaban[10] have both been studied in patients with recent acute coronary syndrome. The doses of rivaroxaban studied were low (2.5 mg twice daily and 5 mg twice daily) and these doses are not currently available in Australia. In combination with aspirin and another antiplatelet drug, the low doses of rivaroxaban reduced the composite of death from cardiovascular causes, myocardial infarction, or stroke compared to placebo. There was an increase in intracranial haemorrhage and major bleeding not related to coronary artery bypass grafting, without a significant increase in fatal bleeding with rivaroxaban.

Apixaban was studied in a standard dose (5 mg twice daily) in combination with aspirin or dual antiplatelet therapy. This trial was stopped early due to a significant increase in the rate of major bleeding in the apixaban group, compared to placebo. There was no reduction of cardiac events with apixaban.[10]

The European Society of Cardiology guidelines in 2015 suggested that rivaroxaban 2.5 mg twice daily might be considered in combination with aspirin and clopidogrel for non-ST-elevation myocardial infarction in patients who have high ischaemic risks but low bleeding risks. Caution is needed in patients more than 75 years of age or less than 60 kg bodyweight.[11]

Patients with a pre-existing indication for anticoagulation

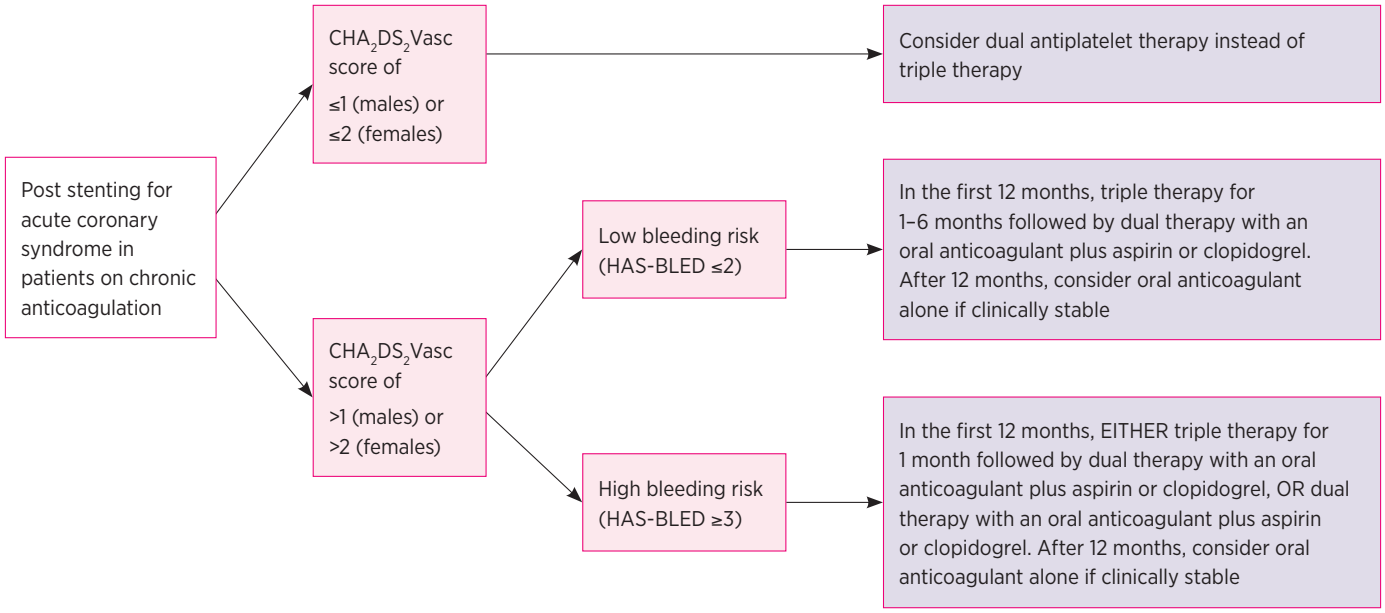
For patients with acute coronary syndrome who have been managed without intracoronary stenting (by medical management, fibrinolytic therapy, or coronary artery bypass graft surgery), and who also have another indication for chronic anticoagulation (e.g. atrial fibrillation), it is usual to use a single antiplatelet drug and an oral anticoagulant. After one year, if the patient has had no further coronary events, it is reasonable to stop the antiplatelet drug and continue the oral anticoagulant. The strength of evidence for this recommendation is low, but it is common practice.

There are no randomised trials comparing an oral anticoagulant in combination with a single antiplatelet drug to an oral anticoagulant and dual antiplatelet therapy in patients without coronary stents. A brief period of oral anticoagulants and dual antiplatelet therapy for 1–3 months is reasonable in selected patients who are at low risk of bleeding, but have a particularly high risk of recurrent ischaemic events.

Anticoagulation after coronary stent insertion

Nowadays patients with acute coronary syndromes are often managed with a percutaneous coronary intervention, predominantly by intracoronary stent placement. Long-term antiplatelet therapy is required to prevent stent thrombosis, but some patients may also require anticoagulation (see Fig. 2).

Fig. 2 **Suggested approach for patients requiring chronic anticoagulation after intracoronary stenting**



There is no evidence for the use of apixaban in this setting.
CHA_2DS_2Vasc and HAS-BLED scores see reference 5

Patients with a pre-existing indication for anticoagulation

About 5–10% of the patients scheduled for coronary artery stenting are already taking oral anticoagulants, usually for atrial fibrillation.[12] Until recently, the suggested approach for these patients was to take aspirin, clopidogrel and an oral anticoagulant (triple therapy) for 1–6 months following the insertion of a drug-eluting stent, then stop one of the antiplatelet drugs. $P2Y_{12}$ antagonists other than clopidogrel (ticagrelor and prasugrel) are not recommended for triple therapy due to higher bleeding rates.

The WOEST study[13] was the first trial comparing dual versus triple therapy after insertion of coronary stents. Patients who were receiving long-term oral anticoagulants and undergoing percutaneous intervention were randomised to warfarin plus clopidogrel alone (dual therapy) or warfarin plus clopidogrel and aspirin (triple therapy). The treatment was for at least one month following bare-metal stenting and for 12 months following drug-eluting stenting. The primary outcome of bleeding was significantly higher in the triple therapy group (44.4% vs 19.4%). The combined secondary end point of death (myocardial infarction, stroke, target-vessel revascularisation, and stent thrombosis) was lower with dual therapy (11.1% vs 17.6%).

There is considerable interest in optimising strategies following coronary stent placement using the non-vitamin K oral anticoagulants, with studies of rivaroxaban and dabigatran now available.

The PIONEER AF-PCI trial[14] studied 2124 patients with non-valvular atrial fibrillation who had undergone percutaneous coronary intervention with stenting to one of three antithrombotic regimens. Patients were randomised in a 1:1:1 ratio to:

- low-dose rivaroxaban (15 mg daily) plus a $P2Y_{12}$ inhibitor for 12 months
- very-low-dose rivaroxaban (2.5 mg twice daily) plus dual antiplatelet therapy
- dose-adjusted warfarin plus dual antiplatelet therapy.

The primary outcome of clinically significant bleeding occurred less commonly in the two groups receiving rivaroxaban. There was no significant difference in the incidence of ischaemic cardiovascular events in the three groups, but the trial was underpowered for this end point so firm conclusions about efficacy cannot be drawn.[10] Many clinicians are concerned that low-dose rivaroxaban may not provide sufficient protection against stroke in patients with atrial fibrillation.

The RE-DUAL trial[15] involved 2725 patients with atrial fibrillation who had undergone percutaneous intervention. They were randomised to:

- triple therapy with warfarin plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and aspirin (for 1–3 months)
- dual therapy with dabigatran (110 mg or 150 mg twice daily) plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor).

Both dabigatran groups had a significantly lower incidence of major or clinically relevant non-major bleeding. Dual therapy was non-inferior to triple therapy with warfarin for thromboembolic events.

Recruitment is currently underway for the AUGUSTUS trial comparing apixaban and warfarin in patients with atrial fibrillation undergoing percutaneous intervention. The primary outcome will be the rate of major bleeding.

The trials appear to show that dual therapy (oral anticoagulant plus one antiplatelet drug) is a reasonable option after stent insertion for patients with an indication for anticoagulation, particularly in those patients with a high bleeding risk.

Patients without a pre-existing indication for anticoagulation

There have been a number of studies examining the role of warfarin compared to antiplatelet drugs to prevent stent thrombosis in patients without another indication for oral anticoagulants. The largest of these showed a higher rate of stent thrombosis in patients receiving either aspirin alone or warfarin and aspirin compared to dual antiplatelet therapy with aspirin and ticlopidine.[16] Based on this and on other trials with concordant results, dual antiplatelet therapy is recommended to prevent stent thrombosis following stent placement in the absence of another indication for oral anticoagulation. It should be noted that these trials used early-generation stents that were associated with a higher rate of stent thrombosis than contemporary stents.

Anticoagulation in stable coronary artery disease

Stable coronary artery disease includes patients who are asymptomatic following an acute coronary syndrome, patients with transient episodes of angina or demonstrable ischaemia precipitated by a reversible mismatch of myocardial supply and demand, and asymptomatic patients with known atherosclerotic disease confirmed by invasive or CT coronary angiography. It is common practice to use a single antiplatelet drug in these patients, but 5–10% will have recurrent events each year.[17]

The role of oral anticoagulants in secondary prevention was recently explored in the COMPASS trial.[18] This trial randomly assigned 27 395 participants with stable atherosclerotic vascular disease to receive rivaroxaban (2.5 mg twice daily) plus aspirin, rivaroxaban alone (5 mg twice daily), or aspirin alone. The incidence of the primary outcome (composite of cardiovascular death, stroke, or myocardial infarction) was lower with rivaroxaban 2.5 mg plus aspirin compared with aspirin alone (4.1% vs 5.4%, hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.66–0.86, P<0.001) but with more major bleeding events (3.1% vs 1.9%, HR 1.70, 95% CI 1.4–2.05). While it is not yet used in routine practice for patients with stable coronary artery disease, oral anticoagulation might have a role in selected patients with a high risk of ischaemic events but a low bleeding risk.

The optimal long-term antithrombotic treatment of patients with atrial fibrillation and stable coronary artery disease is unresolved. It is common practice to add antiplatelet therapy to anticoagulation. However, a retrospective observational study reported that the addition of an antiplatelet drug to warfarin therapy is not associated with a reduction in the risk of recurrent coronary events or thromboembolism. The risk of bleeding was increased significantly when aspirin (HR 1.5, 95% CI 1.23–1.82) or clopidogrel (HR 1.84, 95% CI 1.11–3.06) was added to warfarin.[19]

For patients with atrial fibrillation who need anticoagulation and have either asymptomatic stable coronary artery disease or a high risk of bleeding, it would be reasonable to use oral anticoagulants alone.

Conclusion

Recent trials have explored the use of oral anticoagulants in patients with coronary artery disease. While there is an expanding role for oral anticoagulants with or without antiplatelet drugs, the bleeding risk is significant. Treatment must be tailored to the patient after careful consideration of harm versus benefit, and a clear plan conveyed to patients and their entire health team.

Conflict of interest: none declared

REFERENCES

1. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86. https://doi.org/10.1136/bmj.324.7329.71
2. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502. https://doi.org/10.1056/NEJMoa010746
3. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213-60. https://doi.org/10.1093/eurheartj/ehx419
4. de Araújo Gonçalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. Eur Heart J 2005;26:865-72. https://doi.org/10.1093/eurheartj/ehi187
5. Lane DA, Lip GY. Use of the CHA_2DS_2-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. Circulation 2012;126:860-5. https://doi.org/10.1161/CIRCULATIONAHA.111.060061
6. Fox KAA, Lucas JE, Pieper KS, Bassand JP, Camm AJ, Fitzmaurice DA, et al; GARFIELD-AF Investigators. Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. BMJ Open 2017;7:e017157. https://doi.org/10.1136/bmjopen-2017-017157
7. Merlini PA, Bauer KA, Oltrona L, Ardissino D, Cattaneo M, Belli C, et al. Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. Circulation 1994;90:61-8. https://doi.org/10.1161/01.CIR.90.1.61
8. Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. Eur Heart J 2006;27:519-26. https://doi.org/10.1093/eurheartj/ehi485
9. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, et al; ATLAS ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366:9-19. https://doi.org/10.1056/NEJMoa1112277
10. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, et al; APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med 2011;365:699-708. https://doi.org/10.1056/NEJMoa1105819
11. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267-315. https://doi.org/10.1093/eurheartj/ehv320
12. Schömig A, Sarafoff N, Seyfarth M. Triple antithrombotic management after stent implantation: when and how? Heart 2009;95:1280-5. https://doi.org/10.1136/hrt.2008.160457
13. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, et al; WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013;381:1107-15. https://doi.org/10.1016/S0140-6736(12)62177-1
14. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016;375:2423-34. https://doi.org/10.1056/NEJMoa1611594
15. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al; RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377:1513-24. https://doi.org/10.1056/NEJMoa1708454
16. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, et al; Stent Anticoagulation Restenosis Study Investigators. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. N Engl J Med 1998;339:1665-71. https://doi.org/10.1056/NEJM199812033392303
17. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, et al; REACH Registry Investigators. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA 2010;304:1350-7. https://doi.org/10.1001/jama.2010.1322
18. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017;377:1319-30. https://doi.org/10.1056/NEJMoa1709118
19. Lamberts M, Gislason GH, Lip GY, Lassen JF, Olesen JB, Mikkelsen AP, et al. Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant: a nationwide cohort study. Circulation 2014;129:1577-85. https://doi.org/10.1161/CIRCULATIONAHA.113.004834

DENTAL NOTE

Dentistry concerns for patients taking anticoagulants and antiplatelet drugs

Paul Sambrook
Chair, Dental Therapeutics Committee, Australian Dental Association, Sydney

Aust Prescr 2018;41:116
https://doi.org/10.18773/austprescr.2018.040

Dentists must be aware of all patients who are being treated with oral anticoagulants or antiplatelet drugs. Some patients may be taking anticoagulants in combination with antiplatelet drugs. There should be an understanding as to why these drugs have been prescribed.

The risk of coronary events has to be weighed against the risk of bleeding.[1,2,3] The regimen will have been individualised with a careful assessment of each patient's risk of thrombosis and bleeding to find the optimal balance between harm and benefit. In most instances of dental treatment, the regimen should not be interfered with as this could place the patient at greater risk.

For simple surgical procedures such as the extraction of a single tooth or scaling and cleaning, alteration of the regimen is not required. After an extraction local measures such as haemostatic material supplemented by a suture is all that is needed.

If more extensive surgery is contemplated then a risk assessment in conjunction with the patient's medical practitioner must be undertaken. If it is felt that the risk of stopping the drugs is great, surgery must be modified. Is the risk of not having the surgery greater than the risk of cardiovascular events? Can the surgery be spread over a number of appointments? If surgery cannot be postponed or split into shorter sessions, inpatient management would generally be required.

After surgery the patient must be given explicit, written instructions. The patient must be watchful for unusual or prolonged bleeding and know where and how to receive advice and help.

The message here is that stopping the drugs is often more risky than the issue of bleeding. In most instances minor surgery combined with local haemostatic measures is required. If alteration of the antithrombotic regimen is required, this must be done in a monitored and controlled environment.

Conflict of interest: none declared

REFERENCES

1. Breik O, Cheng A, Sambrook P, Goss A. Protocol in managing oral surgical patients taking dabigatran. Aust Dent J 2014;59:296-301. https://doi.org/10.1111/adj.12199
2. Oral and dental. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2018. www.tga.org.au [cited 2018 Jul 1]
3. Tran H, Joseph J, Young L, McRae S, Curnow J, Nandurkar H, et al. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. Intern Med J 2014;44:525-36. https://doi.org/10.1111/imj.12448

Australian Prescriber
VOLUME 41 : NUMBER 4 : AUGUST 2018

ARTICLE

Brief interventions for alcohol and other drug use

SUMMARY

Brief interventions essentially include screening and assessment of all patients about their alcohol or other drug use. This then allows the clinician to provide information and advice to reduce the harms associated with risky use.

These interventions are generally opportunistic and are offered to people who have not sought assistance but have been identified through routine screening.

Brief interventions are more effective in people who are 'at risk' of developing dependence rather than those who are already dependent or experiencing severe drug-related harms.

The effectiveness of brief interventions in the real-world setting has been questioned in recent years.

Brief interventions should be repeated whenever possible rather than focusing on a single session.

Craig Rodgers
Senior staff specialist, Alcohol and Drug Service, St Vincent's Hospital, Sydney

Keywords
alcohol use, binge drinking, brief intervention, drug dependence

Aust Prescr 2018;41:117–21
https://doi.org/10.18773/austprescr.2018.031

Introduction

'5 minutes is as good as 20' is what we often say when we discuss brief interventions for alcohol and drug misuse. But what exactly are brief interventions and are they really effective?

Alcohol and other drug use is of particular concern in Australia. The 2016 National Drug Strategy Household survey revealed that 17% of Australians aged 12 years or older drank harmful levels of alcohol.[1] This equates to drinking more than two standard drinks (10 g of alcohol) per day. In addition, 36% had consumed five or more standard drinks on a single occasion at least once in the past year. This exceeds the National Health and Medical Research Council single occasion risk guidelines.[2]

We know that alcohol carries a significant burden of disease costing the Australian economy at least $15 billion.[3,4] The cost of illicit drug use is also high at approximately $8 billion per year.[3]

History

Brief interventions can be traced back to work done in the early 1960s in Boston and London at roughly the same time.[5] The Boston intervention involved a psychiatrist and a social worker seeking to capitalise on the emergency care visit by referring the patient to out-patient alcohol treatment. The intervention involved 'meeting patients initially with understanding, sympathy and attention to expressed needs, however concrete they may be'. The London study is widely credited as being a seminal influence on ending abstinence as the exclusive goal of alcohol treatment and recognising controlled drinking as being an acceptable outcome.[5]

Further work in 2003 saw the development of the Screening, Brief Intervention, and Referral to Treatment (SBIRT) tool. This was developed in the USA for healthcare settings to address the full spectrum of unhealthy alcohol and drug use, including those with more severe alcohol-related conditions.[6]

What are brief interventions?

The World Health Organization (WHO) defines brief interventions as 'practices that aim to identify a real or potential alcohol (or other drug) problem and motivate an individual to do something about it'.[5] They include screening and assessment, which then allows the clinician to provide information and advice to reduce risky alcohol or other drug consumption and related problems.[7] They are generally opportunistic and are offered to people who have not sought treatment or assistance but have been identified through routine screening.[7]

Brief interventions aim to inform people that they are drinking or using drugs at levels that increase their risk of developing abuse or dependence disorders and to encourage them to decrease consumption to reduce risk.[7] They are not usually effective in people who have developed dependence or who are experiencing severe drug-related harms. More intensive treatment interventions by drug and alcohol specialist services are recommended for these people.[7]

How and when are brief interventions conducted?

While brief interventions have largely focused on primary care settings, any healthcare professional with adequate training can conduct them. Practice nurses in particular may be more suited due to the time constraints of GPs and may be more cost effective.[8]

Using computers to deliver screening tools has also been touted as more viable than pen-and-paper questionnaires.[8] The internet and mobile devices provide new possibilities for standalone or facilitated interventions,[9] and would also offer benefits such as greater validity and anonymity.

When to undertake brief interventions is also an area of confusion. They can readily be performed in the following scenarios:[10]

- all new patients
- health assessments
- chronic disease assessments, for example hypertension, diabetes, gastro-oesophageal reflux disease, abnormal liver function tests.

Repeating brief interventions whenever possible rather than focusing on a single session, has been argued to improve efficacy.[6,11]

Just as brief interventions originated in the emergency department, this should also be a logical place to deliver them. However, more recent research has shown that even with 'booster sessions' by telephone after an emergency department visit, brief interventions did not improve outcomes at 12 months.[12]

Do brief interventions work?

Many trials and meta-analyses indicate that brief interventions are efficacious as secondary prevention strategies, particularly when targeting alcohol consumption. A meta-analysis in 1997 found that heavy drinkers were twice as likely to have lowered their consumption 6–12 months after a brief intervention than those who received no intervention.[13] Similarly, a WHO study conducted in eight countries (>1600 participants) found that brief interventions reduced daily alcohol consumption by 17% and intensity of drinking by 10%.[14]

Brief interventions were also hailed as reducing alcohol-related problems, healthcare use and treatment costs, and the number of emergency department admissions.[8] A meta-analysis in 2007 of 22 trials identified an overall reduction in drinking of almost four Australian standard drinks (38 g) per week at one year.[15] An updated meta-analysis now including 34 studies in 2018 still showed evidence of a reduction in drinking one year after a brief intervention but this had reduced to the equivalent of two Australian standard drinks (20 g).[16]

In more recent years the effectiveness of brief interventions in the real-world setting has been questioned.[6,9,10] While the 2007 meta-analysis was reassuring in some ways, there were clinically meaningful uncertainties including a major sex difference with men reducing their mean alcohol intake by six standard drinks whereas women only reduced their intake by one standard drink.[10,15] The more recent review in 2018 now shows that both men and women reduce their drinking equally after receiving a brief intervention.[16] It was also disputed that the 2007 review found that trials reporting the largest effects did not take place in primary care or were at high risk of bias. In addition, other large UK general practice trials of brief interventions for alcohol found no benefit.[17,18]

Practical resources to support brief interventions

A critical barrier to implementing brief interventions is the failure to screen and detect individuals at risk of developing alcohol and other drug problems.[8] In general practice, this has been linked to limited access to resources, lack of time, heavy workloads, lack of confidence and concerns about raising sensitive or private issues. Some GPs simply feel that responding to alcohol and other drug issues is not a legitimate part of their work.[4,8]

There are several frameworks now in place to guide clinicians on appropriate screening or assessment. One of the earlier frameworks is summarised as 'FLAGS' – Feedback, Listen, Advice, Goals, Strategies (Table 1). An alternative acronym such as 'FRAMES' (Feedback, Responsibility, Advice, Menu of options, Empathy, Self-Efficacy) may also be used.[7]

A more recent framework supported by the Royal Australian College of General Practitioners is the '5As' – Ask, Assess, Advise/Agree, Assist, Arrange (Table 2).[19]

While these frameworks are useful to guide clinicians on how to structure brief interventions, they still need other tools when trying to assess if alcohol or other drug use is causing harm.

A simple but useful tool for engaging patients in discussion about their alcohol use is the AUDIT-C, which is a modification of the Alcohol Use Disorders Identification Test[10] (Table 3). While it might seem impersonal to be using tools such as these, the assessment process itself may be the 'active ingredient' of brief interventions and may explain why longer interventions are no better than shorter ones.[10]

The AUDIT-C is a useful tool for assessing alcohol use, however it may be more difficult to assess for other

Table 1 **FLAGS brief intervention tool for alcohol problems**

Feedback	Provide individualised feedback about the risks associated with continued drinking, based on current drinking patterns, problem indicators and health status. Discuss the potential health problems that can arise from risky alcohol use.
Listen	Listen to the patient's response. This should spark a discussion of the patient's consumption and how it relates to the general population consumption and any false beliefs held by the patient.
Advice	Give clear advice about the importance of changing current drinking patterns and a recommended level of consumption. A typical 5–10 minute brief intervention should involve advice on reducing consumption in a persuasive but non-judgmental way. Advice can be supported by self-help materials that provide information about the potential harms of risky alcohol consumption and can provide additional motivation to change.
Goals	Discuss the safe drinking limits and assist the patient to set specific goals for changing patterns of consumption. Instil the optimism in the patient that his or her chosen goals can be achieved. It is in this step, in particular, that motivation-enhancing techniques are used to encourage patients to develop, implement and commit to plans to stop drinking.
Strategies	Ask the patient to suggest some strategies for achieving these goals. This approach emphasises the individual's choice to reduce drinking patterns and allows them to choose the approach best suited to their own situation. The individual might consider setting a specific limit on alcohol consumption, learning to recognise the antecedents of drinking, and developing skills to avoid drinking in high-risk situations, pacing one's drinking and learning to cope with everyday problems that lead to drinking.

Source: reference 7

drug use and this may be due to the clinician's lack of knowledge of certain drugs. Useful sources about other drugs include:

- Your Room – a place to get facts about alcohol or other drugs https://yourroom.health.nsw.gov.au/Pages/home.aspx
- Alcohol and Drug Foundation https://adf.org.au/drug-facts.

There are also more nuanced tools to guide the assessment process such as the Severity of Dependence Scale (SDS)[20] (Box 1), or more recently the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST-Lite).[21] The SDS was devised to provide a short, easily administered scale to measure the degree of dependence to different types of drugs. The SDS contains five items, all of which are explicitly concerned with psychological components of dependence, including impaired control over drug taking and preoccupation and anxieties about drug use. The SDS score is related to behavioural patterns of drug taking that are, in themselves, indicators of dependence, such as dose, frequency of use, duration of use, daily use and degree of contact with other drug users. It also shows validity in that drug users

Table 2 **The 5As framework for preventive care**

Ask	Identify patients with risk factors
Assess	Level of risk factor and its relevance to the individual in terms of health Readiness to change Health literacy
Advise/Agree	Provide written information Brief advice and motivational interviewing Negotiate goals and targets (including a lifestyle prescription)
Assist	Develop a risk factor management plan that may include lifestyle education tailored to the individual (e.g. based on severity of risk factors, comorbidities) and pharmacotherapies Support for self-monitoring
Arrange	Referral to allied health services or community programs Phone information/counselling services Follow-up, prevention and management of relapse

Reproduced with permission from The Royal Australian College of General Practitioners from Smoking, nutrition, alcohol, physical activity (SNAP): a population health guide to behavioural risk factors in general practice, 2nd ed. Melbourne: The Royal Australian College of General Practitioners; 2015. p. 6–7. Available at www.racgp.org.au/your-practice/guidelines/snap[19]

Table 3 **AUDIT-C questionnaire for engaging patients about their alcohol use**

Questions	Score
How often do you have a drink containing alcohol?	
Never	+0
Monthly or less	+1
2–4 times per month	+2
2–3 times per week	+3
4 or more times a week	+4
How many standard drinks containing alcohol do you have on a typical day?	
1 or 2	+0
3 or 4	+1
5 or 6	+2
7 or 9	+3
10 or more	+4
How often do you have six or more drinks on one occasion?	
Never	+0
Less than monthly	+1
Monthly	+2
Weekly	+3
Daily or almost daily	+4

Risky drinker: Male – AUDIT-C ≥5 Female – AUDIT-C ≥4

Reproduced with permission from The Royal Australian College of General Practitioners from Tam CW, Knight A, Liaw ST. Alcohol screening and brief interventions in primary care: evidence and a pragmatic practice-based approach. Aust Fam Physician 2016;45:767–70. Available at www.racgp.org.au/afp/2016/october/alcohol-screening-and-brief-interventions-in-primary-care-evidence-and-a-pragmatic-practice-based-approach[10]

Box 1 **Severity of Dependence Scale for assessing the degree of drug and alcohol dependence**

In the past month...

Have you ever thought your [named drug] use was out of control?

Never (0) Sometimes (1) Often (2) Always (3)

Has the thought of not being able to get any [named drug] really stressed you at all?

Never (0) Sometimes (1) Often (2) Always (3)

Have you worried about your [named drug] use?

Never (0) Sometimes (1) Often (2) Always (3)

Have you wished that you could stop?

Never (0) Sometimes (1) Often (2) Always (3)

How difficult would you find it to stop or go without?

Not difficult (0) Quite difficult (1) Very difficult (2) Impossible (3)

Score ≥4 is positive for substance dependence
Source: adapted from reference 20

who have sought treatment at specialist and non-specialist services for drug problems have higher SDS scores than non-treatment samples. Essentially higher total scores indicate higher levels of dependence, although it is recognised that a score of 4 or more is positive for substance dependence.[20]

The ASSIST-Lite tool may be suitable for primary care scenarios, in particular for drugs such as amphetamines, as it was designed to be an ultra-rapid screening tool for substance use disorders.[21] It generally assesses drug use over the last three months and covers a range of substances. Box 2 highlights its use for amphetamines.

Conclusion

While recent evidence suggests there may be reason to question whether brief interventions work in routine clinical practice, in some individuals they will certainly make a difference.[10] A pragmatic approach would be to ensure that all patients are asked about drug and alcohol use in the first instance. This then allows for further assessments to determine current harms. Advice can be given if their use is harmful and goals for change can be established. This should be repeated at every chance you can. At the very least, it may help start a conversation with someone who may then reflect on their behaviour and consider making some positive changes in their life. <

Conflict of interest: none declared

Box 2 **ASSIST-Lite tool for assessing recent drug use (stimulants)**

In the past 3 months...

1. Did you use an amphetamine-type stimulant, or cocaine, or a stimulant medication not as prescribed?

Yes (1) No (0)

If YES

2. Did you use a stimulant at least once each week or more often?

Yes (1) No (0)

3. Has anyone expressed concern about your use of a stimulant?

Yes (1) No (0)

Score ≥2 is positive for substance dependence.
Source: adapted with permission from reference 21

REFERENCES

1. Australian Institute of Health and Welfare. National Drug Strategy Household Survey 2016: detailed findings. Drug Statistics series no. 31. Cat. no. PHE 214. Canberra: AIHW; 2017. https://www.aihw.gov.au/reports/illicit-use-of-drugs/2016-ndshs-detailed/contents/table-of-contents [cited 2018 Jul 1]
2. National Health and Medical Research Council. Australian guidelines to reduce health risks from drinking alcohol. Canberra: Commonwealth of Australia; 2009. https://www.nhmrc.gov.au/guidelines-publications/ds10 [cited 2018 Jul 1]
3. Collins DJ, Lapsley HM. The costs of tobacco, alcohol and illicit drug abuse to Australian society in 2004/05. Canberra: Commonwealth of Australia; 2008. http://www.health.gov.au/internet/drugstrategy/publishing.nsf/content/mono64 [cited 2018 Jul 1]
4. Pennay A, Lubman DI, Frei M. Alcohol: prevention, policy and primary care responses. Aust Fam Physician 2014;43:356-61.
5. McCambridge J, Cunningham JA. The early history of ideas on brief interventions for alcohol. Addiction 2014;109:538-46. https://doi.org/10.1111/add.12458
6. Glass JE, Andréasson S, Bradley KA, Finn SW, Williams EC, Bakshi A-S, et al. Rethinking alcohol interventions in health care: a thematic meeting of the International Network on Brief Interventions for Alcohol & Other Drugs (INEBRIA). Addict Sci Clin Pract 2017;12:14. https://doi.org/10.1186/s13722-017-0079-8
7. Haber P, Lintzeris N, Proude E, Lopatko O. Guidelines for the treatment of alcohol problems. Canberra: Commonwealth of Australia; 2009. http://www.alcohol.gov.au/internet/alcohol/publishing.nsf/Content/guidelines-treat-alc-09 [cited 2018 Jul 1]
8. Roche AM, Freeman T. Brief interventions: good in theory but weak in practice. Drug Alcohol Rev 2004;23:11-8. https://doi.org/10.1080/09595230410001645510
9. McCambridge J, Saitz R. Rethinking brief interventions for alcohol in general practice. BMJ 2017;356:j116. https://doi.org/10.1136/bmj.j116
10. Tam CW, Knight A, Liaw ST. Alcohol screening and brief interventions in primary care: evidence and a pragmatic practice-based approach. Aust Fam Physician 2016;45:767-70.
11. Jonas DE, Garbutt JC, Amick HR, Brown JM, Brownley KA, Council CL, et al. Behavioral counseling after screening for alcohol misuse in primary care: a systematic review and meta-analysis for the US Preventive Services Task Force. Ann Intern Med 2012;157:645-54. https://doi.org/10.7326/0003-4819-157-9-201211060-00544
12. Bogenschutz MP, Donovan DM, Mandler RN, Perl HI, Forcehimes AA, Crandall C, et al. Brief intervention for patients with problematic drug use presenting in emergency departments: a randomized clinical trial. JAMA Intern Med 2014;174:1736-45. https://doi.org/10.1001/jamainternmed.2014.4052
13. Wilk AI, Jensen NM, Havighurst TC. Meta-analysis of randomized control trials addressing brief interventions in heavy alcohol drinkers. J Gen Intern Med 1997;12:274-83. https://doi.org/10.1007/s11606-006-5063-z
14. WHO Brief Intervention Study Group. A cross-national trial of brief interventions with heavy drinkers. Am J Public Health 1996;86:948-55. https://doi.org/10.2105/AJPH.86.7.948
15. Kaner EFS, Dickinson HO, Beyer FR, Campbell F, Schlesinger C, Heather N, et al. Effectiveness of brief alcohol interventions in primary care populations. Cochrane Database Syst Rev 2007:CD004148. https://doi.org/10.1002/14651858.CD004148.pub3
16. Kaner EFS, Beyer FR, Muirhead C, Campbell F, Pienaar ED, Bertholet N, et al. Effectiveness of brief alcohol interventions in primary care populations. Cochrane Database Syst Rev 2018:CD004148. https://doi.org/10.1002/14651858.CD004148.pub4
17. Butler CC, Simpson SA, Hood K, Cohen D, Pickles T, Spanou C, et al. Training practitioners to deliver opportunistic multiple behaviour change counselling in primary care: a cluster randomised trial. BMJ 2013;346:f1191. https://doi.org/10.1136/bmj.f1191
18. Kaner E, Bland M, Cassidy P, Coulton S, Dale V, Deluca P, et al. Effectiveness of screening and brief alcohol intervention in primary care (SIPS trial): pragmatic cluster randomised controlled trial. BMJ 2013;346:e8501. https://doi.org/10.1136/bmj.e8501
19. Smoking, nutrition, alcohol, physical activity (SNAP): a population health guide to behavioural risk factors in general practice. 2nd ed. Melbourne: Royal Australian College of General Practitioners; 2015. https://www.racgp.org.au/your-practice/guidelines/snap [cited 2018 Jul 1]
20. Gossop M, Darke S, Griffiths P, Hando J, Powis B, Hall W, et al. The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. Addiction 1995;90:607-14. https://doi.org/10.1046/j.1360-0443.1995.9056072.x
21. Ali R, Meena S, Eastwood B, Richards I, Marsden J. Ultra-rapid screening for substance-use disorders: the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST-Lite). Drug Alcohol Depend 2013;132:352-61. https://doi.org/10.1016/j.drugalcdep.2013.03.001

FURTHER READING

World Health Organization. Management of substance abuse. Screening and brief intervention for alcohol problems in primary health care. Geneva: WHO; 2003. http://www.who.int/substance_abuse/activities/sbi/en [cited 2018 Jul 1]

Centers for Disease Control and Prevention. Planning and implementing screening and brief intervention for risky alcohol use: a step-by-step guide for primary care practices. Atlanta, Georgia: Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities; 2014. https://www.cdc.gov/ncbddd/fasd/alcohol-screening.html [cited 2018 Jul 1]

SAMHSA-HRSA Center for Integrated Health Solutions. SBIRT: Screening, Brief Intervention, and Referral to Treatment. https://www.integration.samhsa.gov/clinical-practice/sbirt [cited 2018 Jul 1]

MEDICINAL MISHAP

Communication and ciprofloxacin-associated acute kidney injury

Krishna Tirumala-Echampati
Advanced trainee in Renal Medicine

Darren M Roberts
Nephrologist and Clinical pharmacologist

Renal Medicine, Canberra Hospital and Community Services

Aust Prescr 2018;41:122
https://doi.org/10.18773/austprescr.2018.035

Case

A 61-year-old man was transferred from a rural hospital for investigation and management of anuric acute kidney injury. His medical history included recurrent unprovoked deep vein thrombosis, hyperlipidaemia, alcohol use (3–4 cans of beer/day) and gastritis. His usual drugs were apixaban, fenofibrate and pantoprazole.

Two weeks before presenting to the rural hospital, the patient was prescribed ciprofloxacin for a urinary tract infection with *Pseudomonas aeruginosa*. At the time of dispensing he was advised to take the ciprofloxacin 'on an empty stomach'. In response to this advice, the patient decreased his overall daily intake to occasional toast and 3–4 cans of beer. At this time the patient also developed twice-daily watery stools, but he adhered to what he understood to be a food and fluid restriction and continued taking his medicines.

The patient presented to the rural hospital following a fall, complaining of abdominal distension and diarrhoea. Initial observations and investigations found that he was haemodynamically stable with acute kidney injury (serum creatinine over 500 micromol/L) and decreased urine output. The anuria persisted despite fluid resuscitation so the patient was transferred to a specialist centre where his renal function slowly recovered.

Comment

The cause of acute kidney injury in this patient may have been multifactorial, including dehydration from decreased oral intake, diarrhoea and ciprofloxacin-induced nephrotoxicity. Case reports of ciprofloxacin-induced acute kidney injury have proposed multiple mechanisms, including interstitial nephritis, rhabdomyolysis or crystallisation within the renal tubules causing intra-renal obstruction.

A US study found that in men aged 40–85 years old current fluoroquinolone use (at the time of admission, or within seven days) had a 2.18-fold (95% confidence interval 1.74–2.73) higher relative risk of acute kidney injury compared with patients prescribed amoxicillin and azithromycin. This risk was not associated with recent use (prescription completed 8–60 days previously) or past use (>60 days previously).[1] However, the absolute increase in acute kidney injury was low with only one additional case per 1529 patients, or per 3287 prescriptions dispensed.

According to the Australian Medicines Handbook ciprofloxacin should be taken either one hour before or two hours after meals and patients should drink plenty of fluids. This is because the drug's absorption is decreased when it is taken with metallic compounds (notably calcium, iron and aluminium),[2] and due to reports of acute kidney injury from ciprofloxacin-induced crystalluria.

The patient recalled being informed that ciprofloxacin should be taken on an empty stomach, but not about the timing of food intake or the importance of hydration. The decrease in oral intake, coupled with diarrhoea, contributed to volume depletion and the onset of acute kidney injury.

Recommendation

Clear and patient-centred communication reduces misunderstanding and confusion and improves adherence. Patient education is key in this process and may include both verbal and written information. An explanation of why ciprofloxacin is taken separately from food, but not water, may have helped in this case.

Darren Roberts is Chairman of the Editorial Executive Committee of Australian Prescriber.

REFERENCES

1. Bird ST, Etminan M, Brophy JM, Hartzema AG, Delaney JA. Risk of acute kidney injury associated with the use of fluoroquinolones. CMAJ 2013;185:E475-82. https://doi.org/10.1503/cmaj.121730
2. Stojkovic A, Tajber L, Paluch KJ, Djuric Z, Parojcic J, Corrigan OI. Biopharmaceutical characterisation of ciprofloxacin-metallic ion interactions: comparative study into the effect of aluminium, calcium, zinc and iron on drug solubility and dissolution. Acta Pharm 2014;64:77-88. https://doi.org/10.2478/acph-2014-0007

BOOK REVIEW

Therapeutic Guidelines: Neurology. Version 5

Melbourne: Therapeutic Guidelines Limited; 2017. 209 pages
Also available at www.tg.org.au

This edition is packed full of useful and current information presented in a concise and easy-to-read format. All the major topics are covered by experts in the field and supplemented with tables, illustrations and flow diagrams to help make management easier.

It includes the new seizure classification, current stroke guidelines, as well as differentiation of peripheral versus central dizziness. I particularly like the headache and facial pain chapter. Headaches are a complex area with many subtypes, all with their own treatments. As there is no single treatment option for headaches, guidelines like these are needed to demystify the syndromes and treatment options.

The multiple sclerosis chapter offers a helpful two-page table summarising the immunotherapy options, their adverse effects and disease efficacy. Since the publication of this book, there has been another new antibody, ocrelizumab, approved for relapsing remitting multiple sclerosis and the first ever treatment for primary progressive multiple sclerosis. I am sure this will be in the next edition. I note however, that the multiple sclerosis drugs have not been included in the pregnancy and breastfeeding table at the back of the book, which I think would be beneficial.

In the movement disorder section, I was particularly pleased to see a section on how to manage Parkinson's disease in patients who are nil by mouth for a short period of time. I also liked the conversion table for rotigotine patches.

I would highly recommend this edition to all doctors looking for an accurate, quick reference guide centred around Australian practice.

Camilla Jozwik attended a Sanofi Genzyme multiple sclerosis leadership summit in Sydney last year. The flights, accommodation and food were fully paid for by Sanofi Genzyme.

Camilla Jozwik
Neurology advanced trainee, Liverpool Hospital, Sydney

Aust Prescr 2018;41:123
https://doi.org/10.18773/austprescr.2018.038

NEW DRUGS

New drugs

Aust Prescr 2018;41:124
https://doi.org/10.18773/austprescr.2018.041
First published 12 June 2018

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

Atezolizumab

Approved indication: non-small cell lung cancer
Tecentriq (Roche)
vials containing 1200 mg/20 mL as concentrate
Australian Medicines Handbook section 14.2.1

The immune checkpoint inhibitors such as nivolumab and pembrolizumab are being increasingly used to treat non-small cell lung cancer. Atezolizumab is a checkpoint inhibitor that binds to programmed death ligand-1 to prevent it interacting with its receptors. This stops the suppression of the immune response to tumour cells which is a feature of some cancers. Atezolizumab is expected to enhance the response of T-lymphocytes against non-small cell lung cancer.

The drug should be diluted then slowly infused intravenously. Infusions are given every three weeks with a steady state being reached in 6–9 weeks. As atezolizumab is a monoclonal antibody it is likely to be catabolised. There have been no pharmacokinetic studies in patients with hepatic or renal impairment. The elimination half-life is 27 days.

A phase II trial enrolled 287 patients with locally advanced or metastatic non-small cell lung cancer which had progressed after platinum-based chemotherapy. They were randomised to 1200 mg atezolizumab or docetaxel (75 mg/m^2) every three weeks. The median follow-up was approximately 15 months. Progression-free survival was similar for atezolizumab and docetaxel (2.7 vs 3 months), but there was a significant difference in overall survival. Patients given atezolizumab lived for a median of 12.6 months compared with 9.7 months for the docetaxel group.[1]

A similar phase III trial randomised 1225 patients to the same regimen of atezolizumab and docetaxel. The primary efficacy analysis was limited to the first 850 patients. After a median follow-up of 21 months, 569 patients had died. Median overall survival was 13.8 months with atezolizumab and 9.6 months with docetaxel. This advantage was independent of tumour histology (squamous vs non-squamous) and the expression of the programmed death ligand.[2]

Infusing an antibody that affects the immune response has some predictable adverse reactions. In addition to infusion reactions, these include a risk of pneumonitis, hepatitis, colitis, neuropathy, meningoencephalitis, myocarditis and pancreatitis. Some of these immune-related reactions to atezolizumab can be fatal. In the phase III trial, treatment-related adverse events were less frequent than with docetaxel (64% vs 86%). Common complaints included fatigue, nausea, diarrhoea and musculoskeletal pain. Adverse events led to a change in dose for 25% of the atezolizumab group (36% with docetaxel) and 8% withdrew from treatment (19% with docetaxel).[2]

Although atezolizumab has an advantage in overall survival, compared to docetaxel, experience with the drug is limited. The median duration of treatment in the phase III trial was 3.4 months. Most patients do not respond as the objective response rate was only 14% for atezolizumab and 13% for docetaxel.[2] There will need to be more research into predicting which patients will benefit and which will not. For example, atezolizumab may be less favourable for patients with certain mutations, such as an epidermal growth factor receptor mutation.[2] The relative effectiveness of the drugs in the class is currently unclear. Like other immune checkpoint inhibitors, atezolizumab will be studied at different stages of the disease and in other cancers, such as urothelial carcinoma.

T T manufacturer provided additional useful information

REFERENCES

1. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, et al; POPLAR Study Group. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837-46. https://doi.org/10.1016/S0140-6736(16)00587-0
2. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al; OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65. https://doi.org/10.1016/S0140-6736(16)32517-X

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.

Ocrelizumab

Aust Prescr 2018;41:125–6
https://doi.org/10.18773/austprescr.2018.028
First published 12 June 2018

Approved indication: multiple sclerosis

Ocrevus (Roche)
vials containing 300 mg/10 mL concentrate
Australian Medicines Handbook section 16.5

Multiple sclerosis is an autoimmune disease caused by immune cells attacking the central nervous system resulting in demyelination. Commonly the disease has a relapsing-remitting course, but some patients have a more progressive type of multiple sclerosis. During the past 20 years immunotherapy has been increasingly used to reduce rates of relapse.[1] The available options include genetically engineered monoclonal antibodies, such as alemtuzumab and natalizumab which target different parts of the immune system. Ocrelizumab is a monoclonal antibody that binds to the CD20 antigen on B lymphocytes. The resulting lymphocyte depletion modulates the immune response, but the exact mechanism of action of ocrelizumab in multiple sclerosis is currently uncertain.

Ocrelizumab concentrate has to be diluted and then slowly infused intravenously. The recommended regimen is to give half the usual dose then repeat the infusion after two weeks and then give the usual dose (600 mg) every six months. As an antibody, ocrelizumab is subsequently cleared by catabolism. It has a terminal elimination half-life of 26 days.

In a phase II placebo-controlled trial, 220 patients were randomised to receive high- or low-dose ocrelizumab or interferon beta-1a. These patients had the relapsing-remitting type of multiple sclerosis and their response to treatment was primarily assessed by the number of gadolinium-enhancing lesions seen on MRI of the brain. After 24 weeks the mean number of new lesions was 6.6 in the placebo group, 7.2 in the interferon group and 0.8 with both doses of ocrelizumab. Ocrelizumab also reduced the total number of lesions significantly more than placebo or interferon.[2] The lower dose (600 mg) regimen was used in the subsequent phase III trials.

Two trials (OPERA I and II) compared ocrelizumab infusions with subcutaneous interferon beta-1a in 1656 patients with relapsing multiple sclerosis. When these patients were assessed after 24 weeks there was a lower risk of disability progression in the ocrelizumab group. At 96 weeks the annualised relapse rate was lower with ocrelizumab. MRI revealed that the total number of new or enlarged lesions in the brain was also significantly lower (see Table).[3]

There are currently no effective treatments for primary progressive multiple sclerosis. The efficacy of ocrelizumab for this condition was compared with placebo infusions in 732 patients. They were treated for at least 120 weeks, but the primary end point of the trial was the progression of disability at 12 weeks. It progressed in 32.9% of the 488 patients given ocrelizumab and in 39.3% of the 244 given placebo. The corresponding figures at 24 weeks were 29.6% and 35.7%. There was a small reduction (3.4%) in the volume of lesions seen on MRI in patients given ocrelizumab while there was an increase (7.4%) with placebo.[4]

Drugs that reduce the immune response expose patients to an increased risk of infection or reactivation of previous infections. Patients should be screened for hepatitis B before treatment. In the clinical trials, herpes infections and upper respiratory tract infections were more frequent with ocrelizumab than with interferon beta-1a.[3] Immunomodulation can increase the risk of cancer. In the OPERA trials of relapsing multiple sclerosis, four cancers developed in patients taking ocrelizumab compared with two in the interferon groups.[3] Similar to rituximab, another CD20 antibody, ocrelizumab may reduce neutrophil counts. Immunoglobulins are decreased and live vaccines are not recommended. Some patients develop antibodies to ocrelizumab. Infusion-related reactions are common and can be life-threatening.

Table **Efficacy of ocrelizumab in relapsing multiple sclerosis**

Trial	Numbers of patients		Annualised relapse rate at 96 weeks	Proportion with disability progression at 24 weeks	Proportion with no evidence of disease activity at 96 weeks	Total mean number of new or newly enlarged brain lesions at 96 weeks
OPERA I	Ocrelizumab	410	0.16	5.9%	47.9%	0.32
	Interferon beta-1a	411	0.29	9.5%	29.2%	1.41
OPERA II	Ocrelizumab	417	0.16	7.9%	47.5%	0.33
	Interferon beta-1a	418	0.29	11.5%	25.1%	1.90

Source: reference 3

NEW DRUGS

Patients need to be given steroids and antihistamines before ocrelizumab is infused.

The drug should not be used in pregnancy and conception should be avoided for at least six months after stopping treatment. The safety of ocrelizumab in lactation is unknown.

Ocrelizumab is approved for primary progressive and relapsing forms of multiple sclerosis. There are now at least 10 drugs available to manage the relapsing forms. Some require injection, others can be taken by mouth. Other monoclonal antibodies have reduced relapse rates more than interferons, so the results of the ocrelizumab trials are not surprising. An analysis, supported by rival pharmaceutical companies, calculated the numbers of patients who need to be treated to prevent one relapse, relative to interferon therapy. These were four or five for alemtuzumab and eight for ocrelizumab. To prevent one patient having worsening disability at six months requires 13–15 to be treated with alemtuzumab and 21–23 to be treated with ocrelizumab.[5] In primary progressive disease ocrelizumab does have advantages over placebo, but some of them are small and not significant.[4] No cases of progressive multifocal leucoencephalopathy appeared in the clinical trials, but the long-term safety and efficacy of ocrelizumab will require further study to establish its place in therapy.

REFERENCES

1. Taylor I, Coleman J. Treatment of multiple sclerosis with newer immune-modulating drugs. Aust Prescr 2002;25:32-5. https://doi.org/10.18773/austprescr.2002.033
2. Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet 2011;378:1779-87. https://doi.org/10.1016/S0140-6736(11)61649-8
3. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al; OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2017;376:221-34. https://doi.org/10.1056/NEJMoa1601277
4. Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, et al; ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017;376:209-20. https://doi.org/10.1056/NEJMoa1606468
5. Comi G, Alroughani R, Berkovich R, Limmroth V, Macdonell RAL, Moreau T. Number needed to treat analyses to assess clinical outcomes in patients with relapsing-remitting multiple sclerosis treated with alemtuzumab or ocrelizumab (P6.384). Neurology 2017;88:(Suppl 16).

T manufacturer provided the product information

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.

Palbociclib

Aust Prescr 2018;41:127–8
https://doi.org/10.18773/austprescr.2018.029
First published 12 June 2018

Approved indication: breast cancer

Ibrance (Pfizer)
75 mg, 100 mg or 125 mg capsules
Australian Medicines Handbook Appendix A

Palbociclib is indicated for people with advanced breast or metastatic cancer that is hormone-receptor positive (oestrogen and/or progesterone) and human epidermal growth factor receptor 2 (HER2)-negative. It is a small molecule inhibitor of cyclin-dependent kinases 4 and 6 and the first in its class to be approved in Australia. These kinases are involved in signalling pathways that lead to cell proliferation and their activity is increased in hormone-receptor-positive breast cancers.

When used as initial therapy, palbociclib should be given in combination with an aromatase inhibitor such as letrozole. However, in women who have progressed on previous endocrine-based therapy, it should be given with the oestrogen receptor antagonist fulvestrant.

The recommended dose of palbociclib is 125 mg with food at around the same time every day. It is given for 21 days of a 28-day cycle. Co-administered letrozole 2.5 mg should be given orally every day of the 28-day cycle and co-administered fulvestrant 500 mg should be given intramuscularly on days 1, 15 and 29 of the first cycle and then once a month after that. Before and during treatment, pre- and perimenopausal women should also be given a gonadotrophin-releasing hormone agonist such as goserelin.

The approval of palbociclib is based on several clinical trials.[1-4] An open-label phase 2 study (PALOMA-1) randomised previously untreated postmenopausal women to palbociclib plus letrozole (n=84) or letrozole alone (n=81). At the final analysis, median progression-free survival was longer in the group receiving combination treatment compared to the group receiving letrozole alone (20.2 vs 10.2 months).[1] Median overall survival was also longer (37.5 vs 34.5 months). In the palbociclib plus letrozole group, 42% of patients had a partial response to treatment and 1% had a complete response. The corresponding response rates in the letrozole-only group were 32% and 1%.[1]

Similar results were found in a double-blind trial (PALOMA-2) of previously untreated postmenopausal women (n=666). Median progression-free survival was longer with palbociclib plus letrozole compared to placebo plus letrozole (24.8 vs 14.5 months).[2]

Another trial enrolled 521 women who had relapsed or progressed despite previous endocrine therapy (PALOMA-3).[3] Unlike PALOMA-1 and -2, this trial compared palbociclib with fulvestrant and included pre- and perimenopausal women, who received concomitant goserelin. Following treatment with palbociclib plus fulvestrant or placebo plus fulvestrant, median progression-free survival was significantly longer in the palbociclib group (9.5 vs 4.6 months).[4]

In women receiving palbociclib and letrozole, the most common adverse events were neutropenia (78.9% of patients), infections (59.6%), leukopenia (40%), fatigue (38%), nausea (34.3%), alopecia (31.1%), stomatitis (29.4%), anaemia (26.4%) and diarrhoea (25.2%). The adverse event profile was similar in women who received fulvestrant with palbociclib.

Although rare, pulmonary embolism was more common in women taking palbociclib (1.15%, 10/872) than in women taking comparator treatments (0.63%, 3/473).[1-3] Eye problems including blurred vision, increased lacrimation and dry eye were also more common (3.4–6.4% vs 0.7–2.7%).

Myelosuppression is a problem with palbociclib. Neutropenia was serious (grade 3 or 4) in two-thirds of the women taking palbociclib in the trials. Complete blood counts need to be monitored before treatment starts, at the beginning of each cycle and on day 15 of the first two cycles. If severe neutropenia develops, the dose should be stopped or reduced, or the next treatment cycle should be delayed.

Following oral administration, maximum serum concentrations are reached in 4–8 hours. Palbociclib is extensively metabolised by oxidation and sulfonation. The drug's elimination half-life is 28.8 hours in patients with breast cancer and the dose is eliminated in the faeces (74.1%) and urine (17.5%). Exposure to palbociclib is increased in renal and hepatic impairment.

Palbociclib is mainly metabolised by cytochrome P450 (CYP) 3A and sulfotransferase enzyme (SULT2A1). Concomitant administration of strong CYP3A inhibitors (e.g. atazanavir, clarithromycin, erythromycin, voriconazole and grapefruit juice) is not recommended. Strong CYP3A inducers (e.g. carbamazepine, phenytoin, rifampicin, St John's wort) should also be avoided. Moderate CYP3A inducers such as efavirenz and modafinil can be used if absolutely necessary.

Palbociclib seems to extend progression-free survival when added to letrozole or fulvestrant in women who have hormone-receptor-positive and HER2-negative advanced or metastatic breast cancer. However, the addition of palbociclib carries the risk of severe and treatment-limiting myelosuppression for the majority of patients.

T manufacturer provided the product information

REFERENCES

1. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015;16:25-35. https://doi.org/10.1016/S1470-2045(14)71159-3
2. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016;375:1925-36. https://doi.org/10.1056/NEJMoa1607303
3. Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med 2015;373:209-19. https://doi.org/10.1056/NEJMoa1505270
4. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17:425-39. https://doi.org/10.1016/S1470-2045(15)00613-0

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

Silodosin

Aust Prescr 2018;41:129–30
https://doi.org/10.18773/austprescr.2018.030
First published 12 June 2018

Approved indication: benign prostatic hypertrophy

Urorec (Mayne)
4 mg and 8 mg capsules
Australian Medicines Handbook section 13.2.1

Benign prostatic hyperplasia can cause lower urinary tract symptoms such as slow urine flow, nocturia and incomplete emptying of the bladder. If these symptoms are sufficiently bothersome as to require treatment, selective alpha-blockers such as alfuzosin and tamsulosin are one option. These drugs block $alpha_1$ adrenoreceptors in the smooth muscle of the prostate and bladder to reduce resistance and so improve urinary flow. Silodosin is another selective alpha-blocker. It has much greater affinity for the $alpha_{1A}$ receptor than the $alpha_{1B}$ receptor found in vascular smooth muscle.

Silodosin is taken once a day with food. The dose is halved if the patient has moderate kidney impairment (creatinine clearance 30–59 mL/min) and silodosin is not recommended for those with severe impairment (creatinine clearance <30 mL/min). Most of the dose is metabolised, but no data are available on the effect of severe hepatic impairment. The terminal half-life of silodosin is about 11 hours. As the metabolism of silodosin involves cytochrome P450 3A4, it should not be used with strong inhibitors of this enzyme system, such as ketoconazole and ritonavir. Silodosin is also a substrate of P-glycoprotein so using it with strong inhibitors (amiodarone, verapamil) of this transporter is not recommended.

The Australian approval of silodosin is mainly based on three randomised trials. Two of them compared silodosin with placebo in a total of 923 men.[1] These patients had an average baseline score of 21.3 on the 35-point International-Prostate Symptom Score (I-PSS). After 12 weeks of treatment this had reduced by 6.4 points in the 466 men who took silodosin 8 mg daily and by 3.5 points in the 457 who took placebo. There was also a significant difference in urine flow rate. Patient satisfaction was higher with silodosin, with 32% of the men who took it being 'delighted, pleased or mostly satisfied' compared with 22.5% of the placebo group.[1]

The third trial compared silodosin with tamsulosin, as well as placebo.[2] In this trial the baseline I-PSS was 19.1. After 12 weeks of treatment it had reduced by a mean of 7.0 points in the 371 men taking silodosin 8 mg daily and by 6.7 points in the 376 taking tamsulosin 0.4 mg. The average reduction for the 185 taking placebo was 4.7 points. The proportions of patients who had an improvement of at least 25% in the I-PSS were 66.8% with silodosin and 65.4% with tamsulosin. These results were significantly better than the 50.8% response rate to placebo. While 44–45% of the men were 'delighted, pleased or mostly satisfied' with the active treatments, only 34% of the placebo group agreed.[2]

Silodosin was generally well tolerated, but caused more adverse effects than placebo. In the placebo-controlled trials, 6.4% of the silodosin group withdrew because of adverse events compared with 2.2% of the placebo group. Problems that were more frequent with silodosin included dizziness, orthostatic hypotension, diarrhoea and headache. A major difference between silodosin and placebo was the adverse effect of retrograde ejaculation (28.1% vs 0.9%).[1] This abnormal ejaculation is thought to be a consequence of the selective blockade of the $alpha_{1A}$ receptors. This specificity should reduce cardiovascular adverse effects, but in the comparative study silodosin did not have significantly different effects from tamsulosin on pulse and blood pressure.[2] Alpha-blockers may cause floppy iris syndrome so the patient's ophthalmologist should be informed when cataract surgery is being planned.

There can be a high placebo response when treating symptoms associated with benign prostatic hyperplasia. The trials controlled for this by only randomising patients who had not responded during a placebo run-in phase. Despite this the differences between silodosin and placebo were small. Although it is statistically significant, a difference of 2–3 points in the I-PSS is only a slight advantage. The mean difference in maximum urine flow rates was 1 mL/second.[1] Such a small advantage over placebo is of questionable value.[3] The overall efficacy of silodosin is non-inferior to tamsulosin, but silodosin is more likely to cause retrograde ejaculation (14.2% vs 2.1%).[2]

[X] manufacturer did not respond to request for data

REFERENCES

1. Marks LS, Gittelman MC, Hill LA, Volinn W, Hoel G. Rapid efficacy of the highly selective $alpha_{1A}$-adrenoceptor antagonist silodosin in men with signs and symptoms of benign prostatic hyperplasia: pooled results of 2 phase 3 studies. J Urol 2009;181:2634-40. https://doi.org/10.1016/j.juro.2009.02.034
2. Chapple CR, Montorsi F, Tammela TL, Wirth M, Koldewijn E, Fernández Fernández E; European Silodosin Study Group. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. Eur Urol 2011;59:342-52. https://doi.org/10.1016/j.eururo.2010.10.046
3. Dawson A. The price of urine. Aust Prescr 1995;18:26-7. https://doi.org/10.18773/austprescr.1995.031

NEW DRUGS

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

Guanfacine hydrochloride

Aust Prescr 2018;41:131–2
https://doi.org/10.18773/austprescr.2018.042
First published 27 June 2018

Approved indication: attention deficit hyperactivity disorder

Intuniv (Shire)

1 mg, 2 mg, 3 mg and 4 mg modified-release tablets

Australian Medicines Handbook section 18.5

Drugs are only one part of the management of attention deficit hyperactive disorder (ADHD) in children and adolescents.[1] If drug treatment is necessary, psychostimulants such as dexamfetamine and methylphenidate are considered. Atomoxetine is another option and sometimes clonidine is used. Like clonidine, guanfacine hydrochloride is an agonist of the alpha$_2$ adrenergic receptor. Its effects in ADHD are uncertain, but guanfacine does not stimulate the central nervous system.

The new product is a modified-release formulation with peak plasma concentrations reached five hours after the dose is taken. It has a half-life of 18 hours and is suitable for once-daily dosing (morning or evening). The target dose is guided by the child's weight. Most of the dose is metabolised and excreted in the urine with 30% excreted as unchanged drug. The metabolism involves cytochrome P450 3A, so there is a potential for interactions with drugs such as ketoconazole and rifampicin. Guanfacine should not be taken with grapefruit juice. It should also not be taken with high-fat food because this significantly increases absorption. The tablets must not be chewed or crushed.

There have been several placebo-controlled studies of guanfacine in children aged 6–17 years. These trials have usually included a dose optimisation phase as the dose of guanfacine needs to be adjusted according to response and adverse effects. Responses were assessed with tools such as the ADHD Rating Scale IV. Some of the studies included patients taking atomoxetine or psychostimulants, but there were no comparative studies when guanfacine was evaluated in Australia.

A review of 10 studies published up to 2013 concluded that the efficacy of guanfacine was significantly better than placebo. However, in some of the studies a benefit was not seen in adolescents (13–17 years).[2]

In a more recent phase III trial, 338 patients were randomised to take guanfacine, atomoxetine or placebo. They had ADHD of at least moderate severity (mean baseline ADHD Rating Scale scores 43–44). The double-blind phase of the trial was 10 weeks for children (6–12 years) and 13 weeks for adolescents (13–17 years). At the end of the trial the scores had reduced by an average of 23.9 with guanfacine, 18.6 with atomoxetine and by 15 with placebo. Approximately 68% of the guanfacine group were judged to have improved compared with 56% of the atomoxetine group and 44% of the placebo group.[3]

An eight-week trial compared guanfacine monotherapy, methylphenidate monotherapy, and the two drugs together. This trial randomised 212 children and adolescents with baseline scores of 35–37 on the ADHD Rating Scale. These scores reduced by 16.7 with guanfacine, 15.8 with methylphenidate and by 18.3 with the combination. According to a Clinical Global Impression rating scale, 69% of the patients taking guanfacine were very much improved compared with 81% for methylphenidate and 91% for combined treatment.[4]

A randomised-withdrawal study assessed the longer term efficacy of guanfacine in 526 patients. Those who responded (68.6%) to open-label treatment entered a 26-week double-blind phase. At week 13 they were randomised to continue treatment or to be switched to placebo. The primary end point of the study was the proportion of patients whose ADHD Rating Scale scores increased by at least 50%. This treatment failure occurred in 64.9% of those switched to placebo and 49.3% of those who continued guanfacine.[5]

Some of the participants in the phase III trials[3,5] took guanfacine in an open-label extension study. These 214 patients were treated for up to two years. The mean score on the ADHD Rating Scale was 36.7 at baseline and had declined by 19.8 points at the end of the study.[6]

In the review of placebo-controlled trials, 12% of the patients taking guanfacine discontinued it because of adverse events, compared with 4% of the placebo group. Somnolence, sedation and fatigue were common reasons for discontinuing.[2] Caution is therefore needed if the patient is also taking drugs that depress the central nervous system, such as sedating antihistamines. Alcohol should be avoided. Other very common adverse effects include headache and abdominal pain. In combination with methylphenidate, guanfacine increases irritability and insomnia.[4]

Like clonidine, guanfacine can lower blood pressure. Hypotension and bradycardia are common adverse effects. When treatment is stopped, pulse and blood pressure can increase and hypertensive encephalopathy has been reported. It is therefore recommended that guanfacine is gradually discontinued rather than stopped abruptly.

Regular measurement of height and weight is recommended during treatment. However, the body mass index of most patients will remain in the same category while taking guanfacine.[6]

NEW DRUGS

A meta-analysis of seven studies found that 59% of patients will benefit from guanfacine, while 33.3% will respond to placebo.[7] Although a small difference in the scores on a rating scale can be statistically significant, there is debate about what is the minimum important clinical difference. Guanfacine is therefore reserved for children and adolescents 6–17 years old who cannot take or who have had an inadequate response to stimulants or atomoxetine.

T manufacturer provided the AusPAR

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

REFERENCES

1. National Health and Medical Research Council. Clinical practice points on the diagnosis, assessment and management of attention deficit hyperactivity disorder in children and adolescents. Canberra: Commonwealth of Australia; 2012. https://www.nhmrc.gov.au/guidelines-publications/mh26 [cited 2018 Jun 26]
2. Elbe D, Reddy D. Focus on guanfacine extended-release: a review of its use in child and adolescent psychiatry. J Can Acad Child Adolesc Psychiatry 2014;23:48-60.
3. Hervas A, Huss M, Johnson M, McNicholas F, van Stralen J, Sreckovic S, et al. Efficacy and safety of extended-release guanfacine hydrochloride in children and adolescents with attention-deficit/hyperactivity disorder: a randomized, controlled, phase III trial. Eur Neuropsychopharmacol 2014;24:1861-72. https://doi.org/10.1016/j.euroneuro.2014.09.014
4. McCracken JT, McGough JJ, Loo SK, Levitt J, Del'Homme M, Cowen J, et al. Combined stimulant and guanfacine administration in attention-deficit/hyperactivity disorder: a controlled, comparative study. J Am Acad Child Adolesc Psychiatry 2016;55:657-66.e1. https://doi.org/10.1016/j.jaac.2016.05.015
5. Newcorn JH, Harpin V, Huss M, Lyne A, Sikirica V, Johnson M, et al. Extended-release guanfacine hydrochloride in 6-17-year olds with ADHD: a randomised-withdrawal maintenance of efficacy study. J Child Psychol Psychiatry 2016;57:717-28. https://doi.org/10.1111/jcpp.12492
6. Huss M, Dirks B, Gu J, Robertson B, Newcorn JH, Ramos-Quiroga JA. Long-term safety and efficacy of guanfacine extended release in children and adolescents with ADHD. Eur Child Adolesc Psychiatry 2018 Feb 13. [Epub ahead of print]. https://doi.org/10.1007/s00787-018-1113-4
7. Ruggiero S, Clavenna A, Reale L, Capuano A, Rossi F, Bonati M. Guanfacine for attention deficit and hyperactivity disorder in pediatrics: a systematic review and meta-analysis. Eur Neuropsychopharmacol 2014;24:1578-90. https://doi.org/10.1016/j.euroneuro.2014.08.001

EDITORIAL OFFICE

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

Postal The Editor
Australian Prescriber
PO Box 104
DEAKIN WEST 2600

Telephone (02) 6202 3100

Fax (02) 6282 6855

Email info@australianprescriber.com

Website nps.org.au/australianprescriber

Twitter @AustPrescriber

SUBSCRIPTIONS

Australian Prescriber is published every two months online. All content is accessible free of charge in full text at nps.org.au/australianprescriber. New drugs are published between issues as they become available.

An email alert can be sent to you when *Australian Prescriber* publishes new material. Subscribe or update your details at nps.org.au/australianprescriber

For back issues, and copies of the Anaphylaxis wallchart and Switching-antidepressants poster, email info@australianprescriber.com

Australian Prescriber

AUSTRALIAN PRESCRIBER IS INDEXED AND ARCHIVED BY

- Academic Search Complete
- Academic Search Research and Development
- Australian Public Affairs Information Service - Health
- EMBASE/Excerpta Medica
- Emerging Sources Citation Index
- PubMed Central

Typesetting by Stripe Design, Canberra
ISSN 1839-3942

Published by NPS MEDICINEWISE

Independent. Not-for-profit. Evidence-based. NPS MedicineWise enables better decisions about medicines, medical tests and other health technologies. We receive funding from the Australian Government Department of Health.