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EDITORIAL

Improving the quality use of highly specialised drugs

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Highly specialised drugs, such as biological therapies, are an increasing challenge for the quality use of medicines (QUM). QUM is a central objective of Australia's National Medicines Policy. The National Strategy for Quality Use of Medicines aims to make the best possible use of medicines to improve health outcomes for all Australians.[1]

To improve QUM the Australian Government has been funding the National Prescribing Service (now called NPS MedicineWise) since 1998 to design, develop, implement and evaluate national programs. From inception, specialist physicians have contributed to NPS MedicineWise programs, for example in developing and endorsing key messages. However, the prescribers of highly specialised drugs have not been a key audience for QUM interventions.

A wide range of interventions has emerged to promote the uptake of research findings and evidence-based practices into routine care.[2] Given their variable success, research continues with a focus on improving the understanding of how to design and evaluate interventions, and identifying factors that modify their effectiveness.

There is no single strategy to suit all circumstances, nor precise guidance on which combinations of interventions are effective. However, systematic reviews report that interventions aimed at individual professionals, such as audit and feedback, educational outreach (academic detailing), use of local opinion leaders and reminders (for drug dosing), are generally effective.[3] These interventions build on undergraduate and postgraduate education.

Audit and feedback are widely used either alone or as a key component of multifaceted interventions. The first national prescriber feedback program was in 1993 by the Department of Veterans' Affairs.[4] This provided GPs with information about their individual patients and their prescribed medicines focusing on potentially hazardous drugs or drug combinations. In 1994, the Health Insurance Commission started providing feedback for GPs, comparing their prescribing to that of their peers.

In 1991 the Drug and Therapeutics Information Service began to operationalise and translate into practice a service using the newly described method of academic detailing. Academic detailing is a term used to describe non-commercial-based educational outreach which involves face-to-face individual education of prescribers by trained healthcare professionals, generally pharmacists. NPS MedicineWise has continued to evolve academic detailing, extending the reach and frequency of programs to create a nationwide educational visiting service in primary care.[5]

NPS MedicineWise draws on the evidence base when designing its key interventions of educational visits (academic detailing), clinical and self-audits, prescriber feedback, and peer-group meetings using practice data and case studies that facilitate problem-based learning. Interventions are complemented by consumer resources, incorporating clear educational messages, for use before, during and after the consultation with a health professional.

Over the past 20 years therapeutics has changed significantly with an increasing number of highly specialised drugs. The Pharmaceutical Benefits Scheme (PBS) has also expanded from subsidising drugs used within the community to include drugs used in public and private hospitals. Most of the top 10 drugs by cost to government are highly specialised drugs[6] which are often listed with restrictions on their use. These restrictions are variably related to specific patient populations, previous therapy, or type of prescriber, but do not specify protocols or treatment pathways. The specified prescribers are usually specialist physicians. This specification allows programs that aim to enhance prescribing to be tailored to these prescribers.

Interventions similar to those used in primary care have not been comprehensively tried or evaluated with specialist-physician prescribers. The Value in Prescribing (ViP) Biological Disease-Modifying Antirheumatic Drugs (bDMARDs) program, funded by the Australian Government, is now testing and evaluating a QUM program for physician specialists in both public and private practice.[7] This program aims to optimise the use of bDMARDs. It will engage directly with physician specialists (particularly rheumatologists, gastroenterologists, dermatologists and immunologists), pharmacists, consumers and hospital drug and therapeutic committees.

A multifaceted approach to QUM for physician specialists using prescribing behaviour change principles has been developed. This will identify priority practice areas for prescribers, research underlying practice issues, and barriers and enablers

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to better practice, and then apply the Theoretical Domains Framework to inform the selection of interventions that are likely to be effective.[8] This framework is used in implementation research to identify influences on health professional and patient behaviour related to implementing evidence-based recommendations. Several theories of behaviour change are clustered into domains providing a framework through which to view the cognitive, affective, social and environmental influences on behaviour. This then supports the selection of appropriate interventions to address the QUM issue.

Within the program, a consortium has been established to ensure an effective multidisciplinary partnership approach with meaningful and timely input of key experts, and perspectives from stakeholders throughout the development cycle. The Targeted Therapies Alliance consortium includes NPS MedicineWise, Arthritis Australia, the Australia and New Zealand Musculoskeletal Clinical Trials Network, Australian Rheumatology Association, Cochrane Musculoskeletal, Council of Australian Therapeutic Advisory Groups (CATAG), Pharmaceutical Society of Australia, Quality Use of Medicines and Pharmacy Research Centre (University of South Australia) and the Society of Hospital Pharmacists of Australia. It works closely with the Australasian College of Dermatologists and the Gastroenterological Society of Australia. By working with these professional groups, the program has gained insights into the expectations of specialist physicians.

The ViP bDMARDs program has developed living evidence-based guidelines, addressing priority clinical questions for specialists. The other components of the program tailored to specialists include educational webinars and podcasts, individualised PBS prescribing feedback reports and educational visits. The program includes complementary interventions for consumers, specialist nurses, pharmacists and drug and therapeutic committees.

Influencing professional prescribing behaviour requires recognising the complex regulatory, policy and organisational context in which clinical decision-making takes place. The program will evaluate audience uptake of program interventions and activities, audience satisfaction, impact on knowledge, intention to change practice and changes to prescribing. To complement these assessments, a realist evaluation will be undertaken. This is a form of theory-driven evaluation, which centres on explaining the causal links between the context in which a program, intervention or policy is implemented and its related outcomes.[9] Explaining prescribing behaviour change and characterising its underlying processes will be important in providing insight into 'what works for whom, why, under which circumstances and to what extent'.[9]

The ViP bDMARDs program seeks to enhance the quality use of highly specialised drugs by working with specialist-physician prescribers using contemporary evidence-based and evaluable processes. Prescribers of highly specialised drugs should benefit from QUM programs, but these need to be carefully tailored to their needs. The outcomes of the ViP bDMARDs program will not be available until 2023. Our experience to date suggests a consortium of stakeholder organisations, with different expertise and interests but agreed goals and roles, is needed when progressing the quality use of highly specialised drugs. ≺

Conflicts of interest: Catherine Hill is a member of the Targeted Therapies Alliance consortium, member of the Pharmaceutical Benefits Advisory Committee, Chair of South Australian Medicines Evaluation Panel, President of Australian Rheumatology Association and has received an educational grant from Vifor Pharmaceuticals. Debra Rowett is a member of the Targeted Therapies Alliance consortium. Jonathan Dartnell is an employee of NPS MedicineWise, which is funded by the Australian Government Department of Health to implement QUM programs.

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LETTERS

Letters to the Editor

Higher dose statins after stroke

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We write with concern regarding the article on drugs in secondary stroke prevention, as it appears to recommend not only statins post-stroke, but high-dose statins.[1]

We checked the references cited including the Cochrane review. This showed that overall, statins confer a relatively marginal 12% relative risk reduction in cerebrovascular events, but no mortality benefit.[2]

Safety data were not discussed, but are particularly relevant in a vulnerable age group. Importantly, there appears to be no specific evidence to support high doses of statins. Clinical guidelines should consider all of the evidence available. In the Heart Protection Study, simvastatin 40 mg daily, which has equivalent efficacy for reducing low-density lipoprotein to 5 mg atorvastatin, reduced ischaemic stroke by about one-quarter, in patients with coronary disease.[3]

A higher statin dose does not appear to reduce stroke further. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, atorvastatin 80 mg daily after a recent stroke reduced stroke by only about one-sixth. It was associated with increased cerebral haemorrhage and more non-cardiovascular deaths.[4] Atorvastatin 80 mg in the Treating to New Targets (TNT) study reduced stroke by almost one-quarter but with a 25% increase in non-cardiovascular deaths.[5]

The number of patients who needed to be treated for one year to prevent one stroke or transient ischaemic attack in SPARCL was 115.[4] The number needed to harm was less than 20 in the large clinical studies. This is an underestimate because patients with any history of adverse effects from statins were excluded. Neither total nor cardiovascular mortality were significantly reduced by higher doses, but more adverse effects were observed.

In recommending statins post-stroke, clinicians need to weigh up clinical trial data and then consider the risks of harm and benefit for the individual patient before deciding whether to prescribe a drug and at what dose.

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Chris Tremonti and Mark Thieben, the authors of the article, comment:

The Stroke Foundation guideline recommends 'All patients with ischaemic stroke or transient ischaemic attack with possible atherosclerotic contribution and reasonable life expectancy should be prescribed a high-potency statin, regardless of baseline lipid levels.'

The risk of haemorrhagic stroke with high-dose statin therapy has been a vexed question in stroke research. In the SPARCL trial[1] the risks were confounded by the low rate of haemorrhagic stroke (55 with high-dose statin and 33 with placebo). This contrasts with 218 ischaemic strokes with statins and 274 with placebo.

A subsequent meta-analysis[2] initially suggested an increased risk of haemorrhagic stroke, however post hoc influence analysis found this was impacted by the largest trial included, which was SPARCL. When SPARCL was excluded from the analysis there

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was no increased risk of haemorrhagic stroke with high-dose statin therapy. This meta-analysis again showed the greatest benefit was from a higher dose statin.

The TNT study was specifically for patients with stable coronary disease.[3] We therefore feel a recent trial is more relevant as it is studying cholesterol management after stroke or transient ischaemic attack.[4]

Given the low incidence of haemorrhagic stroke in SPARCL,[1] the results of the meta-analysis,[2] and the recommendations of the Stroke Foundation, we feel confident recommending careful management of cholesterol after a transient ischaemic attack or stroke. Our practice is to reduce low-density lipoprotein below 1.8 mmol/L.

For patients with large artery disease, for example high-grade carotid stenosis, we recommend high-intensity statins, such as rosuvastatin 20–40 mg or atorvastatin 40–80 mg. The patient's blood pressure should be controlled before starting high-dose statins. In patients without significant large artery disease, our practice has been to use moderate intensity statins such as rosuvastatin 5–10 mg or atorvastatin 10–20 mg.

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Beyond romosozumab

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I am writing in relation to the new drug comment about romosozumab (Evenity),[1] published in *Australian Prescriber*. There is no mention that when treatment with romosozumab is completed transition to an antiresorptive therapy is required to preserve bone mass, as recommended in the Australian approved product information. This states, 'After completing Evenity therapy, transition to an antiresorptive osteoporosis therapy is required to preserve bone mass.' I bring this to the attention of your readers in the interest of the quality use of medicines.

Jeffrey Hassall
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Conflicts of interest: Jeffrey Hassall is employed by Amgen Australia and has stock/stock options in Amgen Inc.

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ARTICLE

Management of hypertension in pregnancy

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Keywords
antihypertensive drugs, blood pressure, hypertension, pre-eclampsia, pregnancy

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SUMMARY

Hypertensive disorders of pregnancy are common and can result in maternal and fetal morbidity and mortality. Women may have chronic hypertension, or develop hypertension during pregnancy.

Management involves close maternal and fetal surveillance. If an antihypertensive drug is needed, prescribe one that is safe in pregnancy.

Pre-eclampsia is a hypertensive disorder of pregnancy. Women at high risk of pre-eclampsia should start aspirin 150 mg daily at 12–16 weeks gestation and continue until 36 weeks gestation, to reduce the risk of preterm delivery.

There are long-term cardiovascular and mortality risks associated with pregnancies complicated by gestational hypertension and pre-eclampsia. Ongoing cardiovascular and metabolic risk surveillance should be undertaken by the woman's general practitioner.

Introduction

In a normal pregnancy, blood pressure falls in the first trimester. The fall reaches a maximum of 10–15 mmHg (systolic) in mid-pregnancy, and returns to pre-pregnancy levels by term. Hypertensive disorders of pregnancy affect approximately 5–10% of pregnancies in Australia. These disorders are associated with both maternal and fetal morbidity and mortality.

Hypertension

Hypertension is defined as a systolic blood pressure 140 mmHg or above, or diastolic blood pressure 90 mmHg or above. This should be confirmed over four hours with repeated measures, or after overnight rest, to determine if there is true hypertension. Severe hypertension is classified as a systolic blood pressure 160 mmHg or above, or a diastolic blood pressure 110 mmHg or above. Severe hypertension (160/110 mmHg or above) requires urgent management in hospital.

Hypertensive disorders of pregnancy can be divided into four categories:

- chronic hypertension
  - primary
  - secondary
- gestational hypertension
- pre-eclampsia and eclampsia
- pre-eclampsia superimposed on chronic hypertension.

Chronic hypertension

Chronic hypertension predates the pregnancy or is first diagnosed before 20 weeks gestation. It includes both primary hypertension and less commonly secondary hypertension, related to an underlying cause, such as kidney disease. Routine testing for secondary causes is not recommended in pregnancy, but should be considered postpartum. For pregnant women with chronic hypertension, the initial recommended tests are:[1-3]

- full blood count
- urea, creatinine and electrolytes
- liver function tests
- uric acid
- urinalysis and microscopy
- urine protein:creatinine ratio (to establish a baseline)
- ECG.

Chronic hypertension is associated with adverse maternal and fetal outcomes:

- superimposed pre-eclampsia – 25%
- preterm delivery – 28%
- fetal growth restriction – 17%
- perinatal death – 4%.[4]

Some women have white-coat hypertension. This is defined as a clinic blood pressure of at least 140/90 mmHg, but with normal blood pressure outside the clinic. It is diagnosed by 24-hour

This article is peer-reviewed

ambulatory blood pressure monitoring or home blood pressure monitoring. White-coat hypertension is not entirely benign and is associated with an increased risk of pre-eclampsia (8%).[5] Generally, treatment is not required if the clinic blood pressure is below 160/110 mmHg and the out-of-office blood pressure remains normal.

Management

Women with chronic hypertension may be taking antihypertensive drugs before conception or conceive while taking them. Some of these drugs are contraindicated or not recommended in pregnancy (Table 1).[6] Table 2 lists oral antihypertensive drugs that are safer in pregnancy.[2,6]

The mainstay of management of chronic hypertension in pregnancy is regular maternal review and strict blood pressure control. Often the physiological fall in blood pressure in the first trimester will allow for a reduction or cessation of antihypertensive drug therapy.

Optimal management includes maintaining the blood pressure around 110–140/85 mmHg, regular assessment for the development of pre-eclampsia and close surveillance of fetal growth and wellbeing. Signs and symptoms suggestive of pre-eclampsia include headache, visual changes, epigastric or right upper quadrant pain and oedema (see Box). Assessment also includes careful blood pressure measurement, ideally using automated office or a liquid crystal sphygmomanometer, and testing for proteinuria. Home blood pressure monitoring may form part of this assessment. Proteinuria is defined as a spot urine protein:creatinine ratio above 30 mg/mmol or urine protein excretion above 300 mg/24 hours. Dipstick urinalysis (automated or visual) is most commonly used to screen for proteinuria, with a 'negative' or 'trace' result being normal. One plus (1+) or more on dipstick is sensitive, but inaccurate and should be further evaluated with a spot urine protein:creatinine ratio.

Table 1 **Antihypertensive drugs to avoid in pregnancy**

Antihypertensive class	Advice	Potential adverse effects	Recommendation
ACE inhibitors	Contraindicated	Teratogenic in the second and third trimester resulting in fetal anuria, oligohydramnios, hypocalvaria, intrauterine growth restriction and patent ductus arteriosus, death	Stop drug ideally before conception or at diagnosis of pregnancy
Angiotensin receptor blockers	Contraindicated	Teratogenic in the second and third trimesters, fetal anuria, oligohydramnios, hypocalvaria, intrauterine growth restriction, patent ductus arteriosus, death	Stop drug ideally before conception or at diagnosis of pregnancy
Diuretics	Avoid	Maternal hypovolaemia, fetal hypoglycaemia, thrombocytopenia, hyponatraemia and hypokalaemia	Use an alternative antihypertensive
Beta blockers (other than labetalol)	Avoid	Fetal bradycardia, intrauterine growth restriction (atenolol)	Use an alternative antihypertensive
Calcium channel antagonists (other than nifedipine and diltiazem)	Avoid	Maternal hypotension and fetal hypoxia	Use an alternative antihypertensive

Table 2 **Antihypertensive drugs that can be safely used in pregnancy**

Antihypertensive drug*	Class/action	Dose	Adverse effects
Labetalol	Beta blocker	100 mg twice a day – 400 mg three times a day	Bradycardia, bronchospasm, headache
Nifedipine controlled release	Calcium channel antagonist	30 mg daily – 60 mg twice a day	Headache (first-dose effect), flushing, tachycardia, peripheral oedema
Methyldopa	Central action	250 mg twice a day – 750 mg three times a day	Depression, dry mouth, sedation, rarely haemolysis and hepatitis
Hydralazine	Vasodilator	25 mg three times a day – 50 mg three times a day	Flushing, headache, lupus-like syndrome
Prazosin	Alpha blocker	0.5 mg twice a day – 5 mg three times a day	Orthostatic hypotension

* Although oxprenolol is safe, it is no longer available in Australia.

Gestational hypertension

Gestational hypertension is the development of hypertension at or after 20 weeks gestation, in the absence of other features of pre-eclampsia (see Box). Gestational hypertension is associated with an increased risk of developing pre-eclampsia (up to 25%, depending on the gestation at presentation), as well as the future development of cardiovascular disease.[1-3] Fetal growth restriction is not typically a feature of gestational hypertension.

Management

Regular blood pressure monitoring is necessary to ensure the blood pressure remains at 110–140/80–90 mmHg. There should be regular assessment for the development of pre-eclampsia and close surveillance of fetal growth and wellbeing. Once the blood pressure is controlled, gestational hypertension may continue to be managed with outpatient care, under close and regular review.

Pre-eclampsia

Pre-eclampsia is a complex multisystem disorder of pregnancy arising from abnormal placentation, resulting in an imbalance of angiogenic and anti-angiogenic factors, oxidative stress and immunological involvement. The maternal response to this is thought to involve systemic vascular endothelial dysfunction. Pre-eclampsia may be superimposed on chronic hypertension, or present as new onset hypertension, arising at or after 20 weeks gestation, with the presence of one or more of the typical clinical features (see Box).[1,2]

Risk factors for pre-eclampsia include maternal age, primiparity, previous pre-eclampsia, multiple gestation, prolonged interpregnancy interval and assisted reproduction therapies. Other factors are underlying renal disease or hypertension, antiphospholipid syndrome, systemic lupus erythematosus, diabetes and a maternal body mass index (BMI) above 30 kg/m^2.

Adverse maternal outcomes include eclampsia, stroke, multiorgan failure, major haemorrhage and death. Fetal complications of pre-eclampsia include growth restriction, preterm delivery, placental abruption and perinatal death.

Management

Whether pre-eclampsia is new onset or superimposed on chronic hypertension, a multidisciplinary approach optimises maternal and fetal outcomes as delivery is the only definitive cure. There is a balance between the welfare of the growing fetus and the ongoing risk of maternal complications. Management should occur at a specialist centre with the required protocols and expertise because inpatient care is usually required.

For severe hypertension urgent management is indicated and drugs are required to rapidly lower blood pressure (Table 3). An infusion of magnesium sulphate can be considered as it reduces the rate of seizure by 50% (Table 4).[7]

Prediction and prevention

A number of options are available in the first trimester for predicting the risk of pre-eclampsia. These include using maternal blood pressure and risk factors or combined prediction models using additional tests of placental growth factor and doppler imaging of the uterine artery. These tests are readily available and consideration needs to be given to how they could be integrated into antenatal care. In Australia, however, the cost effectiveness of combined first trimester screening for pre-eclampsia has yet to be evaluated.

Although there is no current method of preventing pre-eclampsia, aspirin is recommended for women considered to be at high risk because of maternal risk factors or by clinical prediction models. The ASPRE trial used combined first trimester screening and found a 62% reduction in preterm pre-eclampsia at less than 37 weeks gestation in women who took aspirin 150 mg daily.[8] Women at high risk require early obstetric review, because starting aspirin before 16 weeks is most effective. If started for pre-eclampsia prophylaxis, aspirin should be continued until

Box Features of pre-eclampsia and eclampsia

Renal
- proteinuria – spot urine protein:creatinine ratio 30 mg/mmol or more
- acute kidney injury with serum creatinine >90 micromol/L
- oliguria: <80 mL/4 hours

Haematological
- thrombocytopenia – platelet count <100,000/microlitre
- haemolysis
- disseminated intravascular coagulation

Hepatic
- raised serum transaminases (alanine aminotransferase or aspartate aminotransferase >40 IU/L)
- severe right upper quadrant or epigastric pain

Neurological
- eclamptic convulsion
- sustained clonus (hyperreflexia is commonly found and not diagnostic)
- severe headache
- visual disturbance – photopsia, scotomata, cortical blindness
- stroke

Pulmonary oedema

Uteroplacental dysfunction with fetal growth restriction, abnormality on doppler imaging of the umbilical artery, stillbirth

Table 3 **Urgent treatment of severe hypertension* in pregnancy**

Drug	Dose	Route	Onset of action	Adverse effects
Hydralazine	5–10 mg	Intravenous bolus repeated after 20 min if blood pressure remains >160/110 mmHg	20 min	Flushing, headache, nausea, hypotension, tachycardia
Labetalol	20–80 mg	Intravenous bolus over 2 min, repeat after 10 min if blood pressure remains >160/110mmHg	5 min	Bradycardia, hypotension, fetal bradycardia
Labetalol	200 mg	Oral	30–45 min	Bradycardia, bronchospasm, headache
Nifedipine†	10 mg	Oral	30–45 min	Headache, flushing

* Severe hypertension is 160/110 mmHg or above.
† This formulation is no longer available in Australia.

Table 4 **Seizure prophylaxis and treatment of eclampsia**

Drug	Dose	Route	Onset of Action	Adverse effects
Magnesium sulphate	4 g	Intravenous bolus over 20 min followed by 1 g/hour infusion, typically continued for 24 hours	20 min	Flushing, respiratory depression Caution in renal impairment as magnesium is excreted renally and toxicity may occur

36 weeks gestation. Aspirin reduces the risk of preterm birth, fetal growth restriction and fetal death, but may increase postpartum bleeding.[9,10]

Women with an inadequate dietary calcium intake may have an increased risk of pre-eclampsia. They should aim to achieve the recommended daily allowance (1000 mg daily) through diet or calcium supplementation to reduce the risk.[11]

Postpartum management

After delivery, hypertension typically resolves within 12 weeks for women with gestational hypertension or pre-eclampsia. If this does not occur, consideration should be given to investigation for primary or secondary hypertension. Regular monitoring of blood pressure postnatally should occur, with down titration of antihypertensive drugs when the systolic blood pressure drops below 120 mmHg. For women with chronic hypertension, the decision to return to their usual antihypertensive treatment will depend on its compatibility with breastfeeding, and their future pregnancy plans. It would be reasonable to transition them back to their usual treatment early, provided they remain aware of the importance of review before future pregnancies to ensure it will be safe to use.

The antihypertensive drugs that are safe in pregnancy are also safe in breastfeeding. However, given that methyldopa is associated with a 30% risk of depression, it is usually stopped postpartum. ACE inhibitors, particularly enalapril, have very low concentrations in breast milk and are often used during lactation. Angiotensin receptor blockers are not recommended due to a lack of available safety information.

Long-term implications

Gestational hypertension and pre-eclampsia are associated with a two- to fourfold increase in the future risk of cardiovascular disease. Women may develop hypertension, stroke, diabetes, venous thromboembolic disease or chronic kidney disease. Cardiovascular events such as stroke may occur in middle age. Given these risks, and the cumulative risks associated with several pregnancies complicated by severe pre-eclampsia, or preterm delivery, preconception counselling before future pregnancies is recommended.

Women with a history of hypertension in pregnancy require indefinite follow-up. They are recommended to have annual reviews of blood pressure, fasting lipids and blood glucose. Counselling on a healthy lifestyle and diet, maintenance of an optimal BMI, smoking cessation and regular exercise are essential for optimising long-term health outcomes.[12-14] <

Conflicts of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

1. Angiotensin receptor blockers should not be used during pregnancy and lactation.
2. Women at high risk of pre-eclampsia should avoid taking aspirin after the first trimester of pregnancy.

Answers on page 177

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ARTICLE

Optimising oral health in frail older people

SUMMARY

There is a link between oral health and systemic health. Conditions such as dementia and pneumonia are associated with poor oral health.

Frail older people receive regular care from medical and nursing staff but tend not to see dentists regularly or only seek treatment when there is a dental problem. Collaboration between dentists and other health professionals is therefore increasingly important.

Oral health should be assessed regularly. This enables early referral to a dentist.

Anticholinergic drugs, particularly in polypharmacy, can have a profound deleterious effect on salivary function and oral health. A medication review may enable the anticholinergic burden to be reduced.

In addition to regular brushing, oral preventive products may be appropriate in frail older people.

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Introduction

Most oral and dental problems in frail older people may not be obvious to relatives and health professionals. Older people do not see dentists regularly but receive regular care from medical and nursing professionals, so collaboration with dentists is important. This is especially the case in residential aged care. Improved oral health outcomes are achievable using an interdisciplinary approach involving GPs, dentists, oral health therapists, dental prosthetists and nurses trained in oral health.

Relationship between oral and systemic health

There is a link between poor oral health and systemic disease. There are correlations between adequate mastication and activities of daily living, nutritional status and quality of life.

A significant association exists between the severity of periodontal disease, increasing tooth loss and carotid artery plaque.[1] This may increase all-cause mortality in cardiovascular disease including ischaemic stroke.[2]

Chewing increases regional neural activity and cerebral blood flow.[3,4] The number of teeth lost may be a predictor of cognitive decline and dementia.[5-7] The bacteria that cause periodontal disease have been implicated in Alzheimer's disease.[8]

There is an association between oral health and respiratory disease.[9] Randomised controlled trials show that improved oral hygiene reduces the progression or occurrence of respiratory diseases and death from pneumonia among high-risk older adults living in residential care.[10]

Diabetes increases the risk for periodontitis. Periodontal inflammation negatively affects glycaemic control causing systemic complications. Severe periodontitis increases the risk of cardiorenal mortality 3.2 times. Periodontal treatment and better oral hygiene can improve metabolic control.[11]

The importance of saliva

Normal salivary function is essential in speech, digestion and swallowing. Saliva has antimicrobial activity and prevents decay and tooth wear. In healthy people, stimulated saliva has a high serous volume with higher bicarbonate buffering concentrations to neutralise mouth, food and plaque acids compared to resting saliva. High flow volumes are essential for effective buffering capacity, clearance of glucose and bacteria, and swallowing.

In frail older people with decreased salivary function and poor oral hygiene, teeth may rapidly demineralise when not in a supersaturated solution of calcium and phosphate ions provided by saliva. Teeth will also decay more rapidly as mouth pH is unable to return to safe values due to a lack of buffering capacity, particularly if there is frequent snacking on sweet foods and drinks.

Salivary gland hypofunction and dry mouth

GPs should be encouraged to ask patients about a dry mouth. The prevalence of salivary gland hypofunction (measurable decrease in salivary flow) and xerostomia (subjective feeling of dry mouth) increases with age, the number of chronic conditions and is strongly associated with drugs. The prevalence of xerostomia can be over 50% for people taking more than five drugs and it has marked effects on oral health and quality of life.

Hyposalivation can significantly impact activities of daily living such as speaking, eating and sleeping. It may cause tingling, a decreased sense of taste, halitosis and difficulty in wearing dentures. It can increase the risk of opportunistic infections such as *Candida albicans*. Low saliva flow rates correspond to lower mucosal wetness and increase pathogenic aciduric microorganisms in the oropharynx, mouth and dental plaque (which can be inhaled).

Tooth decay in older people

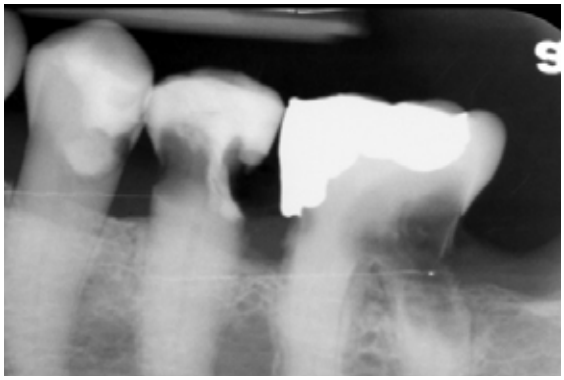
Tooth decay is manageable if treated promptly so early referral is important. Root surface decay is common in older people (Figs 1 and 2). It is more difficult to detect than decay affecting the crowns of the teeth (coronal caries) and progresses much more rapidly. In 10 Sydney residential aged-care facilities, 46% of residents (mean age 86.9 years) had 1–3 decayed teeth and 7% had more than four decayed teeth on entry.[12] In another study of 19 facilities in Melbourne, 68% of residents had coronal caries (mean 2.6) and 77% had root caries (mean 5).[13]

Tooth loss has further effects on nutrition, systemic health, quality of life and the ability to socialise. Every effort should be made to prevent decay progressing to the pulp (nerve) of the tooth. Exposed nerves and root stumps, even when symptom free, act as wicks for oral bacteria to infect bone. This can cause multiple chronic dental abscesses adding to the inflammatory burden of the patient. Treatment may require hospitalisation to remove teeth due to recurring dental infections, when there is a lack of co-operation as in dementia or delirium, or when the airway and swallowing may become compromised during dental procedures (Fig. 3).

Silver fluorides are potent biocides that can prevent and stop caries.[14] They also improve gingival health when applied topically to susceptible teeth every 3–6 months. Drilling is often not required so applications are non-threatening and ideal for frail or fearful patients showing challenging behaviours.

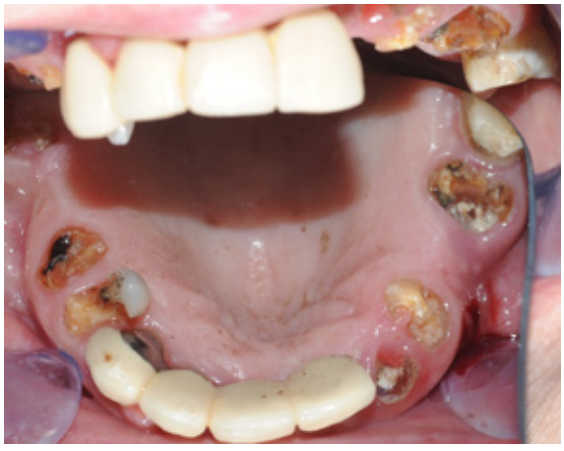
Symptom-free chronic infections in bone, arising from infected nerves or from periodontitis, are common findings on dental radiographs but may not be obvious on a visual examination. If untreated these infections can complicate medical conditions and future management.

Fig. 1 **Root caries**



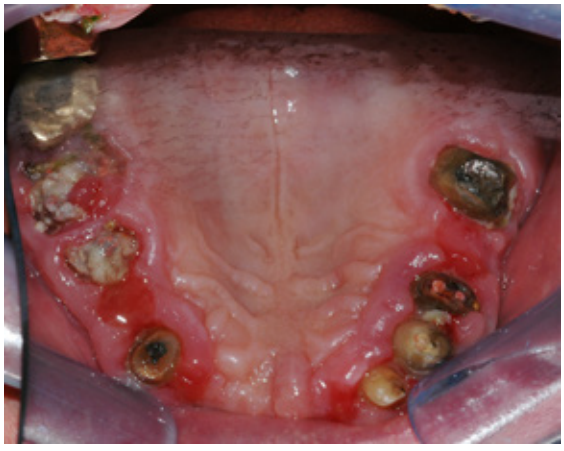
Advanced root caries involving the nerve and extending under the gumline. Crowns will snap off to leave root stumps. Visual examination alone may not be able to detect decay under the gumline and in the back of the mouth.

Fig. 2 **Tooth decay**



Decaying teeth in a relatively clean mouth of a person with dementia. Salivary gland hypofunction may be involved in the progression of decay.

Fig. 3 **Infected root stumps**



Multiple roots stumps with infections in the bone in a patient with dementia. This is a common finding and removing all teeth will require a general anaesthetic.

Drugs can affect oral health

A significant association exists between prescription medicines, saliva function and rapidly progressing multiple decaying teeth.[15] Many drugs prescribed for older patients have anticholinergic activity. These may cause a marked decrease in saliva flow as they prevent parasympathetic (cholinergic) activity at the muscarinic receptors in salivary glands.[16]

Polypharmacy is common in older people.[17] Different classes of drugs have different levels of anticholinergic activity and can add to the overall anticholinergic burden. In general, medicines for urinary incontinence, antidepressants and antipsychotics have the greatest effects and are significantly associated with xerostomia and salivary gland hypofunction.[18-21] In complex cases a medication review with a pharmacist may be appropriate. The anticholinergic burden may be minimised by considering the following:

- Order a medication review and deprescribe when possible.[22]
- Switch to a drug with less anticholinergic activity.[19-21]
- Reduce the dose as anticholinergic effects are dose related.
- Administer drugs during the day rather than at night. Resting saliva is lowest at night and higher during the day.
- Divide the dose into smaller doses throughout the day.
- Check for adverse drug interactions that cause increased drug concentrations due to inhibition of drug metabolism or clearance.

Commonly used drugs with adverse oral effects

Oral adverse drug reactions are common, varying in nature and severity.[23]

The corticosteroid inhalers used in asthma and chronic obstructive pulmonary disease can cause pharyngitis, oral mucositis (ulcerations) and candidiasis particularly in the elderly. The inhalers used to relieve acute asthma, such as salbutamol and terbutaline, are beta$_2$ agonists. They reduce saliva flow and lower its pH causing increased decay rates and tooth wear. Additional adverse reactions are taste alterations, gingivitis and gingival enlargement.[24] Patients should be instructed to rinse and gargle with water after using their inhalers. They should also use a daily fluoride rinse.

Bruxism and dyskinesia are associated with the selective serotonin reuptake inhibitors and antipsychotic drugs. Metoclopramide may be associated with tardive dyskinesia which may persist and be irreversible, especially in older people. Uncontrolled movements of the tongue and lips make denture wearing exceedingly difficult.[23]

Calcium channel blockers, valproate, phenytoin and cyclosporin can cause gingival enlargement. Anticoagulants can cause bleeding from the gums.

Drugs associated with lichenoid sensitivity reactions are non-steroidal anti-inflammatory drugs and antihypertensives, including beta blockers, ACE inhibitors and diuretics.[24] Cutaneous lichenoid hypersensitivity reactions may resemble oral lichen planus.

Rarely, antiresorptive drugs such as bisphosphonates and denosumab can cause osteonecrosis of the jaw. This can be spontaneous from denture trauma, or occur after extractions due to poor bone healing.

It is advisable for GPs to refer patients for dental examinations with dental radiographs before starting bisphosphonates or denosumab, before cardiac or major surgery, and before head and neck radiotherapy. Radiotherapy adversely affects bone healing at extraction sites and markedly decreases saliva function resulting in increased decay rates.

Chemotherapy drugs, such as 5-fluorouracil, cisplatin, methotrexate, and hydroxyurea can cause painful oral ulcers and ulcerative mucositis.[24]

Patient assessment and referral

GPs and residential aged-care nurses should be encouraged to look into patients' mouths to assess oral health. Use a strong light (preferably a headlight) with gauze to wipe teeth and gums, and two dental mirrors. One mirror is used to retract lips and tongue and the other to visualise soft tissues and teeth. These aids greatly assist screening for decaying teeth, ulcers, dental infections and oral cancers. Most oral ulcerations either heal themselves or resolve after simple dental intervention within 2–3 weeks. Any area that persists longer than three weeks may be suspicious.

There is an Oral Health Assessment Tool that can be used by GPs, residential aged-care nurses and allied health professionals, but requires some training to use. It is a validated tool to detect early oral problems and provides guidance on when to refer to a dentist. There are eight categories to assess – lips, tongue, gums and tissues, saliva, natural teeth, dentures, oral cleanliness and pain. They are scored as healthy, changes, unhealthy or needing referral.

Referrals by GPs to dentists should be routine and ideally part of over 75 years of age health assessments or chronic disease management plans. It is often difficult for dentists to obtain a full medical history and medicines list from older patients. Dentists may need to phone GPs to ask about

comorbidities and the patients' medicines, particularly anticoagulant drugs.

Dental referral is also encouraged before receiving a residential or home-care package. The better someone's oral health is before entering a facility, the better their long-term systemic and oral health outcomes will be.

Risk indicators and risk stratification

Patients are evaluated for the risk of:

- oral infections and pain from decaying teeth, root stumps, periodontitis
- aspiration pneumonia from salivary gland hypofunction together with poor swallowing ability and poor oral hygiene
- adequate nutrition from poor chewing ability and denture stability, pain
- psychosocial problems and depression related to poor anterior aesthetics, poor chewing ability or pain.

Assessing a person's degree of risk can help to guide patient management and referral to a dentist (Box 1). Useful oral health screening questions for older people able to self-report are:[25]

- Have you had pain in your mouth while chewing?
- Have you lost any fillings, or do you need a dental visit for any other reason?
- Have you avoided laughing or smiling?
- Have you had to interrupt meals due to dental pain, unstable dentures that hurt, difficulty swallowing, mouth being too dry, inappropriate diet or embarrassment?

Older people who may not be able to self-report may be at very high risk when three or more of these problems occur together:

- not seen a dentist for two or more years
- high-dependency care needs (e.g. requires assistance for activities of daily living, such as toileting, weak grip strength) and unable to physically brush their teeth

Box 1 Maintaining oral care in older people according to risk

Healthy, robust patients

Use fluoride toothpaste containing 1450 parts per million (most toothpastes), twice daily. Fluoride prevents decay and remineralises teeth. Fluoride binds calcium, forming fluorapatite which dissolves at a lower pH.

Use a soft toothbrush. Brushing is very important to mechanically remove biofilm from teeth, gums, tongue and all denture surfaces.

Use an interproximal brush to clean between teeth.

To clean dentures, use mild soap, white vinegar (dilute 1:4 to remove calcific deposits) or cleanser. Leave dentures out at night to dry. Disinfect with commercial denture cleanser 1–2 times per week. Ensure denture cleanser is suitable for plastic or part metal dentures.

High-risk patients

Avoid mouthwashes or swabs containing alcohol, hydrogen peroxide, sodium bicarbonate, lemon and glycerin. Avoid confectionary with citric acid and sweet sticky foods. Discourage fruit juices, sugary drinks, caffeine, and frequency of snacking. Encourage eating of milk and cheese.

Ensure adequate hydration for saliva production – 2–2.5 L fluid a day (minimum 1.6 L/day), frequently and after meals. Note that older people may have an altered urge to drink and may have difficulty swallowing.

Use pea size amounts of high-fluoride toothpaste (5000 parts per million), 1–2 times a day. This remineralises teeth and prevents or slows decay. Do not swallow. Spit but do not rinse so product stays on teeth.

Casein phosphopeptide amorphous calcium phosphate cream (available from dentists) remineralises teeth and is used as an adjunct after fluoride. Use 1–2 times a day. Add water to cream if mouth is dry. Leave a small amount on the teeth and do not rinse. Not suitable if the patient has a milk protein allergy, but can be used if lactose intolerant.

Use sugar-free gum 4–6 times a day after meals. Chewing neutralises mouth and plaque acids, aids in glucose clearance and maintains saliva gland function. Excessive consumption may have a laxative effect.

Frequently use artificial saliva and high pH oral lubricant (should not contain citric acid) on all oral tissues and under dentures for temporary symptomatic relief of dry mouth. Use a water-based moisturiser on lips.

Very high-risk patients (also use same products as with high-risk patients)

Non-staining chlorhexidine gluconate toothpaste (0.05 or 0.12%) at night can be used long term in older people and has prolonged, broad-spectrum antiseptic activity which reduces oral biofilm. Spit out but do not rinse. In some products increased concentrations of chlorhexidine gluconate can stain teeth (reversible), alter taste and increase calculus (tartar) formation. Use 0.5% gel in localised areas or rinse with 0.2% short term for acute infections. As chlorhexidine is deactivated by fluoride in toothpastes, use high-fluoride toothpaste in the morning and chlorhexidine in the evening.

Palliative care patients

Apply water-based lip moisturiser (not petroleum-based). Use spray bottle applications for oral lubricants and alcohol and stain-free 2% chlorhexidine.

Clean teeth with low-strength sodium bicarbonate oral swabs, 2% chlorhexidine gluconate oral swabs (alcohol free), or both, to improve oral health and quality of life.

These interventions can be delivered by nurses or carers after meals and as needed.

- cognitive impairment which interferes with their ability to brush their own teeth
- polypharmacy including medicines with anticholinergic effects
- a sublingual resting saliva pH* below 5.8 (healthy pH 6.8–7.8, acidic 6–6.6, highly acidic <5–5.8), or difficulty wetting a disposable dental sponge micro-brush placed under the tongue for two seconds to wet pH paper outside the mouth.[26]

Oral health in residential facilities

Dentists tend to treat residents only for acute dental problems and not for routine preventive care. Frail older people who cannot maintain their own oral health require daily preventative care best delivered by nurses and carers trained in assisted brushing. This should be supported by regular professional cleanings and fluoride applications by oral therapists. Access to periodic assessments and regular oral care should be emphasised.

It would help if the person's dentist is included in the admission paperwork when they go into an aged-care facility. Currently there is no protocol to notify dentists when their patients enter residential care. Some dental records, particularly dental implant specifications and oral health assessments, including dental X-rays, should be linked into medical records and transferred to the patient's residential aged-care facility. It is important for the dentist to communicate about treatment with the care team at the aged-care facility. For example, aggressive treatment of oral cancers may not be advisable for the very frail. Palliative care may be more appropriate involving only adequate analgesia and a tailored diet.

Maintaining oral care

Preventative oral products can help to reduce oral biofilm, remineralise teeth and improve saliva function and should be tailored to individual risk (Box 1). Many patients and carers often have difficulty understanding the use of multiple products so a simple handout for them is helpful with the appropriate products circled (Table).[27]

Using the resource links shown in Box 2, including the Oral Health Assessment Tool, raises the importance of oral health in a residential facility. There are practical training guides to help nursing staff gain the knowledge and confidence to assess residents and carry out preventive interventions.[28]

Conclusion

GPs are encouraged to look into the mouths of their patients to make oral health assessments and assess dental risk based on frailty and dependency in order to make early referrals to a dentist when required. Topical interventions are recommended based on risk and can prevent tooth decay. Polypharmacy is common in frail older people and some drugs can reduce saliva production. GPs should therefore prescribe drugs with the lowest anticholinergic affects to better maintain saliva function and oral health. <

Conflicts of interest: none declared

* To test sublingual resting saliva, place a disposable dental sponge micro-brush under the tongue for two seconds. It is normal to be able to wet pH paper. If the pH paper cannot be made wet, it is likely the patient has salivary gland hypofunction or lacks adequate hydration at rest.

  Full saliva testing of frail or fearful older people may not be practical. The benefits of saliva testing in this cohort have not been assessed in a randomised controlled trial. However, assessment of sublingual resting saliva pH offers a simple, quantitative and repeatable test of mouth acidity and quality of resting saliva, and can be performed in general practice and residential aged-care settings.[26]

Table **Oral care product list**

Purpose	Product	Brand	Comment
Remineralise teeth and prevent or slow decay	High-fluoride toothpaste (5000 parts per million)	3M Clinpro 5000 (3M) Neutrafluor 5000 (Colgate)	Do not swallow, leave on teeth
	Casein phosphopeptide amorphous calcium phosphate cream	GC Tooth Mousse	Available from dentists Use 1–2 times a day Leave on teeth Adjunct after fluoride
Cleaning between teeth	Interproximal brushes	Ask pharmacist for advice	
Denture maintenance	Liquid soap	Ask pharmacist for advice	Brush all denture surfaces
	Denture cleansers		Disinfect and clean dentures
	White vinegar		Dissolves calcific deposits
Stabilising poor-fitting dentures that cause ulcers and sore spots	Denture adhesive cream/powder/strips	Biotene Dry Mouth Denture Grip Polident For other products ask pharmacist	Reline or remake dentures
Temporary palliative relief of dry mouth	For artificial saliva, use high pH oral lubricant without citric acid	Ask pharmacist for advice	Delivered via oral spray, oral rinse, gel, swabs or dissolving tablets Before bed Before eating On and under dentures As needed
Bleeding gums (gingivitis)	Brush gums with chlorhexidine gluconate toothpaste	Curasept 0.05 or 0.12%	If unable to brush use non-staining, alcohol-free products Long-term use Do not use chlorhexidine with toothpastes containing sodium lauryl sulphate or fluoride Refer to dentist
Hydration	Water		2–2.5 L/day Stop sweet, sticky, fruity drinks
Saliva function	Sugar-free gum		Improves saliva function 4 times a day Excessive use may cause diarrhoea
Ulcers or denture sore spots	Warm saline		3–4 times a day
	Chlorhexidine gluconate gel 0.5%	Curasept ADS 350	Short-term use Localised topical area
	Anti-inflammatory mouth gel or paste	Difflam Ora-Sed Jel Kenalog in Orabase (steroid)	

Adapted from reference 27

Box 2 Resources to support oral health in older people

Oral health care domain: Care of older people toolkit

South Australian Dental Service

Contains links to: Staff portfolio, Professional portfolio, Dental treatment pathway flow chart

Oral Health Assessment Tool video

South Australia Health

Oral health care for older people in NSW: carer support package

NSW Health

Instruction video on assisted brushing in residential aged-care facilities

Dental Rescue, NSW

Instruction video on denture care

Dental Rescue, NSW

Anticholinergic Burden (ACB) Score Calculator

By Rebecca King and Steve Rabino

ACB calculator

Anticholinergic medicines and scores

Reducing ACB risk

The anticholinergic burden: therapeutic brief

Veterans' MATES, Department of Veterans' Affairs

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FURTHER READING

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ARTICLE

Fluoroquinolone antibiotics and adverse events

SUMMARY

Fluoroquinolones are broad-spectrum antibiotics with good oral bioavailability. They are used for the treatment of a wide variety of infections, but there are restrictions on prescribing these drugs.

Epidemiological studies have reported an increased risk of rare adverse effects. These include tendinopathy and tendon rupture, peripheral neuropathy and aortic aneurysm.

Safe prescribing of fluroquinolones requires recognition of patients with risk factors for toxicity. Prompt drug discontinuation is recommended in the event of an adverse reaction.

Practising antimicrobial stewardship by prescribing fluoroquinolones only when alternative drugs are unavailable is also key to limiting adverse events and antibiotic resistance.

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Introduction

Fluoroquinolones are broad-spectrum antibiotics with good oral bioavailability. Their indications include treatment of urinary tract infections, pneumonia, gastroenteritis and gonococcal infections. Worldwide, fluoroquinolone use is increasing and has been associated with rising rates of resistance. However, use remains relatively low in Australia compared to other countries due to restrictions placed on government-subsidised prescribing of fluoroquinolones.[1]

In addition to the emergence of resistance, recent epidemiological studies have shown an association between fluoroquinolones and rare but significant adverse events. These include tendon rupture and aortic aneurysm and dissection.

Mechanism of action and spectrum of activity

The three systemic fluoroquinolones available for use in Australia are ciprofloxacin, norfloxacin and moxifloxacin. Additionally, ofloxacin is available for topical use in bacterial keratitis. Ciprofloxacin and norfloxacin have excellent activity against aerobic Gram-negative organisms, with ciprofloxacin being especially effective against *Pseudomonas aeruginosa*. Moxifloxacin has additional activity against anaerobes and Gram-positive organisms, particularly pneumococci, but lacks activity against *P. aeruginosa*.[2]

Fluoroquinolones exert antimicrobial effects by inhibiting bacterial topoisomerases II and IV. Antibiotic resistance arises from mutations in these target enzymes.[1]

Adverse effects

The adverse effects of fluoroquinolones can be limited by restricting their use to infections that cannot easily be managed with other antibiotics.

Tendinopathy

Fluoroquinolones are associated with a two- to fourfold increased risk of acute tendinopathy (defined as pain or reduced function without rupture) and tendon rupture.[3] The incidence of this adverse effect may be up to 2% in patients aged 65 years and above, compared with a background tendon rupture rate of approximately 0.9% in the general population.[4,5]

The onset of tendinopathy is highest within the first month after drug exposure.[3] The Achilles tendon is most commonly affected, with severe and sudden onset pain being a characteristic clinical presentation. While optimal management of fluoroquinolone-associated tendon disorders is unclear, prompt drug discontinuation is recommended alongside supportive measures such as analgesia and physiotherapy. The majority of patients (90%) are managed non-operatively with recovery taking a median of one month. There are long-term sequelae including difficulty walking, decreased range of motion and pain in up to 10% of patients.[6]

Risk factors for fluoroquinolone-associated tendinopathy are incompletely defined. Most studies report a pooled incidence from a range of fluoroquinolones including those currently unavailable within Australia.[3,7] Older age and concomitant corticosteroid use are identified as risk factors. Corticosteroids are associated with up to a 14-fold

increased risk of rupture.[3] An association with diabetes or renal failure is less clear.

The mechanism of tendinopathy is unknown. One study found that the risk increased with higher cumulative drug exposure, suggesting a dose-dependent relationship.[8] Collagen degradation due to upregulation of matrix metalloproteinases has also been proposed.[3]

Aortic aneurysm and dissection

The evidence associating fluoroquinolone use and aortic aneurysm and dissection is conflicting. A meta-analysis based on four observational studies has suggested a two- to threefold increased risk, with the number of fluoroquinolone courses needed to harm one patient being 1301.[9] Observational studies, however, are affected by residual confounding and surveillance bias. To minimise differences in rates of imaging that may arise between fluoroquinolone-exposed and non-exposed patients, a case-control study of over one million US patients compared the risk of aortic aneurysm and dissection for specific antibiotic indications. Against azithromycin for pneumonia, the risk of aortic aneurysm and dissection was 2.5 times greater, but there was no risk difference when compared against trimethoprim-sulfamethoxazole for urinary tract infection. The absolute rate of aortic aneurysm and dissection was also very low at less than 0.1%. The authors concluded that the benefits of fluoroquinolones may outweigh a rare potential risk of aortic aneurysm and dissection in some patients.[10]

In contrast, another study found no difference in the risk of aortic aneurysm and dissection between fluoroquinolones and other antibiotics typically used for severe infections (such as amoxicillin-clavulanate or cephalosporins). However, there was an increased risk across all types of infection including pneumonia, genitourinary, intra-abdominal, and soft tissue and bone infections. The authors suggested that infection severity may therefore confound the observed association between fluoroquinolone exposure and aortic disease, particularly as fluoroquinolones are often used for more serious infections and in older patients.[11] Alternatively, a surveillance bias toward imaging patients with severe infection may have strengthened the observed association between sepsis and aortic aneurysm and dissection.

A recent retrospective study reported the risk of rupture, surgery and death only in patients admitted with aortic aneurysm or dissection,[12] thus reducing the risk of surveillance bias. It found a 1.8-fold increased risk of 'aortic death' in patients who had taken fluoroquinolones. However, the comparator group was amoxicillin and not a broader spectrum drug, possibly confounding the range of infections for which the two groups of patients were treated.

When aortic aneurysm and dissection are detected, patients should stop the drug immediately and be referred for appropriate observation and surgical intervention. Particular care should be taken in patients with a family history of aneurysm, pre-existing aortic aneurysm, or the presence of other risk factors including Marfan's syndrome or other connective tissue diseases. There is an updated warning in the Australian and international product information for fluoroquinolone antibiotics.[13]

Peripheral neuropathy

A limited number of observational studies suggest that fluoroquinolones increase the risk of peripheral neuropathy, manifesting as numbness or pain, by up to 1.5-fold.[14-16] However, the occurrence of neuropathy in fluoroquinolone-exposed patients is still rare, with an absolute risk increase in a large database study of just 0.02% per year among all patients, and 0.04% per year in those aged 60 years or above.[14] Risk factors for fluoroquinolone-associated neuropathy include increased body mass index, as well as other known causes of neuropathy such as amyloidosis, alcohol abuse, shingles, and Sjögren syndrome. However, the association between neuropathy and fluoroquinolone use, in the database study, remained even in a subgroup analysis excluding patients with these underlying conditions.[14]

The mechanism of neuropathy remains undefined, with case reports describing evidence of small fibre damage on nerve biopsy.[16] It is unclear if symptoms are reversible after stopping the drug.

Retinal detachment

Evidence for an association between fluoroquinolone use and retinal detachment is conflicting. While a Canadian cohort study reported an up to 4.5-fold increased risk of retinal detachment with current fluoroquinolone use,[17] most subsequent studies, including two recent meta-analyses,[18,19] have found no increased risk. One explanation for the findings of the Canadian study was the presence of an older cohort (mean age 61 years) including patients post-cataract surgery which is a known risk factor for retinal detachment.[17]

QTc prolongation and cardiac arrhythmia

The absolute risk of torsades de pointes with fluoroquinolone use is low, equating to 160 additional serious arrhythmias per 1,000,000 antibiotic courses. However, the risk can be increased by hypokalaemia, hypomagnesaemia and drugs that prolong the QTc interval on the ECG.[20] There is a particular risk

associated with moxifloxacin. This drug probably has twice the risk of arrhythmia compared to ciprofloxacin and levofloxacin.[21]

QTc prolongation occurs due to blockade of cardiac delayed rectifier potassium channels. This leads to prolongation of the action potential.[22]

Gastrointestinal effects

Nausea, vomiting, diarrhoea and taste disturbance have been reported to occur in up to 20% of patients treated with fluoroquinolones.[23] Like all antibiotics, fluoroquinolones carry a risk of *Clostridium difficile* infection. Fluoroquinolone-resistant *C. difficile* infections have emerged in response to increased fluoroquinolone prescribing.[24]

Hepatotoxicity with elevation in transaminases is a class effect of fluoroquinolones. Severe hepatotoxicity with acute liver failure is extremely rare, with the exception of trovafloxacin which was withdrawn from the market.[25]

Hyperglycaemia and hypoglycaemia

Observational studies have reported increased risks for hyperglycaemia and hypoglycaemia with fluoroquinolones.[26-28] The risk of hyperglycaemia (2.5-fold) and hypoglycaemia (2.1-fold) is higher with moxifloxacin than with ciprofloxacin (1.9- and 1.5-fold) after adjustment for relevant baseline factors such as diabetic treatment.[28]

The dysglycaemia is thought to be due to sulfonylurea-like effects on the ATP-sensitive potassium channels of pancreatic islet cells.[26]

Central nervous system effects

Fluoroquinolones have been associated with adverse effects on the central nervous system, including psychiatric adverse reactions. These effects have been included in a boxed warning, on the product labels, by the US Food and Drug Administration. The reported adverse reactions include agitation tremor, hallucinations, psychosis and convulsions.

Conclusion

In Australia, fluoroquinolone prescribing is restricted to infections resistant to all other recommended drugs. Serious adverse effects are rare but significant, and include tendinopathy, aortopathy, neuropathy, arrhythmia, hypoglycaemia and hyperglycaemia. Prescribers should be aware of the risk factors for fluoroquinolone toxicity including patients over 60 years and patients with comorbidities or interacting drugs.

Patients should remain vigilant for symptoms such as tendon or abdominal pain and report these promptly. Appropriate patient education and prompt drug discontinuation in the event of an adverse reaction are important considerations when prescribing fluoroquinolones. <

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Approach to the diagnosis of secondary hypertension in adults

SUMMARY

Presentations that should raise suspicion of secondary hypertension include early-onset, severe or resistant hypertension. A suggestive family history or clinical clues can point to a specific secondary cause.

The most common causes and associations are renal disease, primary aldosteronism and obstructive sleep apnoea. Medicines, illicit substances and alcohol may also be responsible.

The assessment of patients begins with history taking and examination, to look for clinical clues. Laboratory tests include electrolytes, urea, creatinine and the aldosterone:renin ratio, urinalysis and the urine albumin:creatinine ratio. Abnormal results should prompt further investigation.

Initial testing for primary aldosteronism is best done before starting potentially interfering antihypertensive drugs. If the patient is already taking interfering antihypertensive drugs that cannot be stopped, the interpretation of the aldosterone:renin ratio must consider the presence of those drugs. Specialist advice can be sought if needed.

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Introduction

Secondary hypertension occurs in approximately 10% of adults with hypertension.[1] There are many possible causes (Table 1). Identifying and treating the cause can potentially cure or markedly improve hypertension and reduce the associated cardiovascular risk.[1,2]

The history and examination may raise suspicion of secondary hypertension. It is important to remember that drugs can cause hypertension. Laboratory tests can help to identify other causes.

Who should be assessed for secondary hypertension?

International and local guidelines differ in their recommendations and prescriptiveness in relation to screening for secondary causes of hypertension. In general, patients with hypertension and any of the following characteristics should be screened:[1,3]

- age of onset less than 40 years
- abrupt onset of hypertension
- abrupt worsening of hypertension despite previously good control
- hypertensive urgency or emergency
- resistant hypertension (blood pressure ≥140/90 mmHg despite the consistent use of three antihypertensive drugs including a diuretic, or a need for four or more drugs to control the blood pressure)
- target organ damage disproportionate to the degree of hypertension
- family history of early-onset hypertension, stroke before the age of 40 years, or primary aldosteronism
- clinical clues
  - hypokalaemia (may occur in primary aldosteronism)
  - higher elevation than expected (>20%) of serum creatinine after starting an ACE inhibitor or angiotensin receptor antagonist (may suggest renovascular hypertension)
  - paroxysmal hypertension or episodes suggestive of catecholamine excess (suggestive of phaeochromocytoma).

All patients suspected of having secondary hypertension should be screened for the common causes and associations. These include renal disease (parenchymal or renovascular), primary aldosteronism, medicines, illicit substances, alcohol and obstructive sleep apnoea. Other, less prevalent causes should only be investigated if there is strong clinical suspicion of a particular disorder, such as coarctation of the aorta. It is important to remember that a lack of adherence to antihypertensive treatment can cause persistent hypertension.

Table 1 **Laboratory tests in the initial investigation of secondary hypertension**

Cause*	Prevalence in unselected hypertensive patients	Clinical clues	Laboratory tests
Renovascular disease†	5%	Acute worsening of renal function after starting an ACE inhibitor or angiotensin receptor antagonist, flash pulmonary oedema, early-onset hypertension in a female, abdominal bruit	Electrolytes and creatinine with eGFR Urinalysis Urine albumin:creatinine ratio
Renal parenchymal disease†	1%	Haematuria, proteinuria, history of recurrent urinary tract infections or obstruction, family history, polycystic kidneys, abdominal mass	Electrolytes and creatinine with eGFR Urinalysis Urine albumin:creatinine ratio
Primary aldosteronism	8%	Hypokalaemia	Aldosterone:renin ratio
Drugs, alcohol and other substances	2%	Drug history, NSAIDs, SNRIs, decongestants, oral contraceptives, bupropion, ciclosporin, tacrolimus, cocaine, amphetamines, caffeine, nicotine, alcohol, liquorice, some herbal supplements	
Cushing's syndrome	<1%	Striae (purplish-red), proximal muscle wasting, easy bruising, thin skin, rapid weight gain, central adiposity, moon facies, buffalo hump, pathologic fracture, diabetes mellitus	Late night salivary cortisol on two occasions Free cortisol in 24-hour urine on two occasions 1 mg overnight dexamethasone suppression test Measuring a morning or random serum cortisol is not recommended owing to a low sensitivity and specificity for Cushing's syndrome
Phaeochromocytoma/ paraganglioma	<1%	Paroxysms or 'spells': headache, palpitations, sweating, pallor, labile blood pressure	Plasma metanephrines
Aortic coarctation †	<1%	Well-developed upper body, hypertension confined to the upper limbs, systolic murmur	
Obstructive sleep apnoea ‡	25%	Snoring, daytime somnolence, morning headache	

eGFR estimated glomerular filtration rate NSAIDs non-steroidal anti-inflammatory drugs SNRIs serotonin noradrenaline reuptake inhibitors
* Other rare causes of secondary hypertension include acromegaly, thyroid dysfunction and primary hyperparathyroidism.
† Laboratory tests should be complemented by imaging.
‡ Obstructive sleep apnoea has a very strong and important association, but may not be a cause of secondary hypertension.

Initial tests for primary aldosteronism

Patients with primary aldosteronism have a higher risk of cardiovascular morbidity and mortality than other age-, sex- and blood pressure-matched patients.[3] Although testing for primary aldosteronism has not been directly linked with mortality benefits, treating primary aldosteronism surgically (by unilateral adrenalectomy) or with specific mineralocorticoid blockade may improve long-term cardiovascular outcomes.[4]

Hypertension is often the only sign of primary aldosteronism. Most patients do not present with the classical feature of hypokalaemia.

Screening for primary aldosteronism is straightforward if the patient has not started antihypertensive therapy. This involves a blood test, in an unfasted patient who has been ambulatory for at least two hours. It measures aldosterone and renin, allowing calculation of the aldosterone:renin ratio.[3] This ratio is important as some patients with primary aldosteronism will have normal concentrations of aldosterone. As hypokalaemia can cause a false-negative ratio, potassium should be concurrently measured.

Reference intervals and screening thresholds for aldosterone, renin and their ratio vary according to the laboratory's method of measurement (laboratories may measure either direct renin or plasma renin activity). The ratio should be interpreted in the context of the absolute values for aldosterone and renin. For example, a raised ratio due to a very high aldosterone with a non-suppressed renin concentration may be more suggestive of secondary hyperaldosteronism due to diuretic use or other causes. The ratio could also be raised because of a very low renin, even if the aldosterone concentration is not as high as is typically seen in primary aldosteronism.

The finding of an increased aldosterone:renin ratio not explained by interfering antihypertensives and confirmed on more than one occasion should prompt referral to a physician with an interest in hypertension, for consideration of confirmatory dynamic testing and specific treatment.

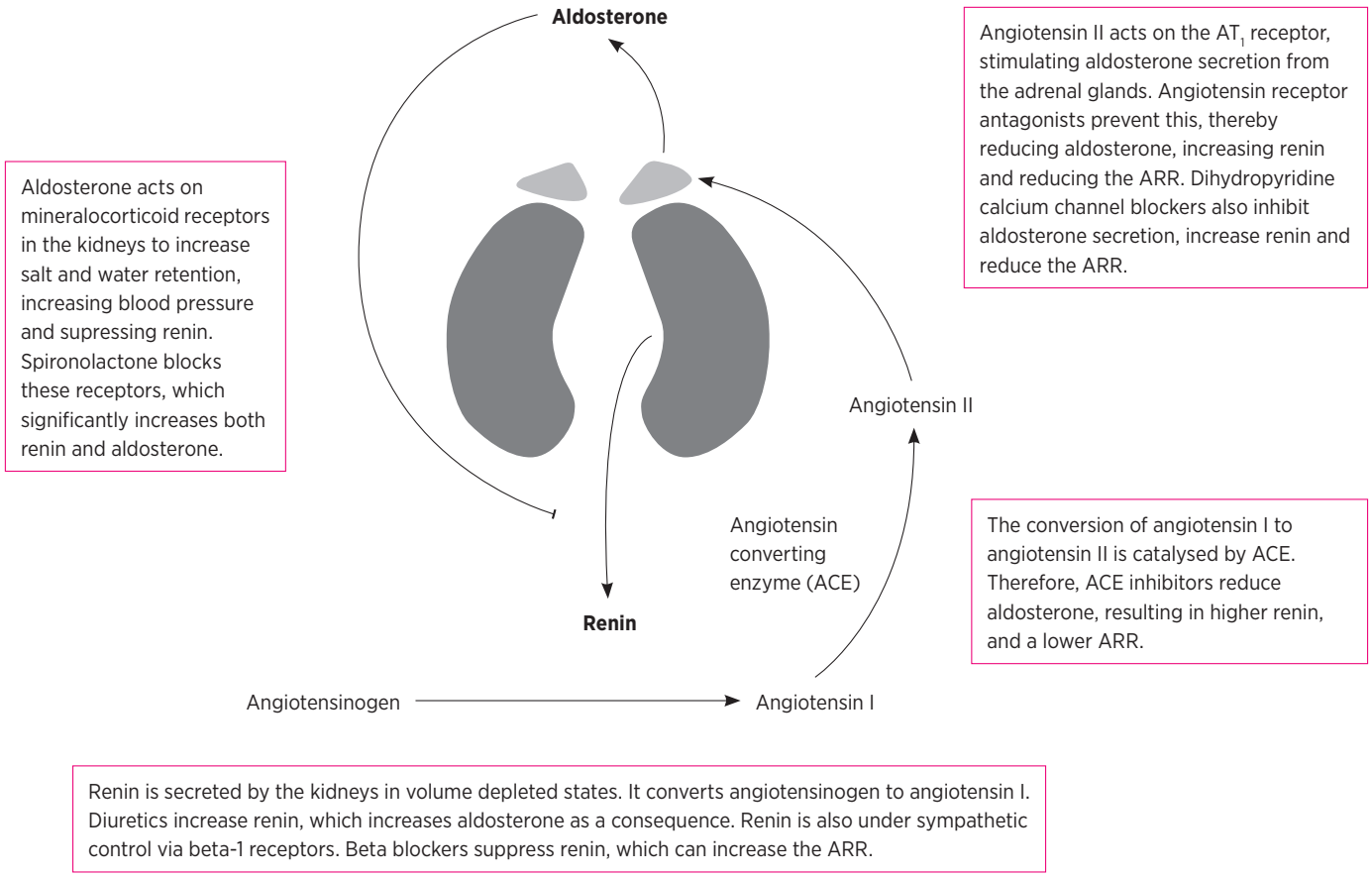
Effect of antihypertensive drugs

Although most antihypertensives affect the plasma concentrations of aldosterone, renin and their ratio (see Fig. and Table 2), additional indications may prevent the suspension of some drugs, such as when a beta blocker is also being used to control an arrhythmia. Initial testing therefore often needs to take place while the patient is still taking interfering antihypertensives. Interpreting an aldosterone:renin ratio while a patient is taking interfering antihypertensives can be difficult. Documenting the patient's antihypertensive drugs on the request form will assist the pathologist's analysis.

A suppressed renin, high aldosterone and raised ratio in a patient taking an ACE inhibitor alone (expected to increase renin and decrease aldosterone) would be suspicious for primary aldosteronism. However, a normal ratio in the same patient would not exclude primary aldosteronism, as it may be a false negative. On the other hand, beta blockers decrease renin concentrations. A patient taking a beta blocker who has a non-suppressed renin concentration probably does not have primary aldosteronism, but a suppressed renin and a raised ratio could be a false-positive result.

Sometimes, substitution of interfering antihypertensives with non-interfering antihypertensives is required to obtain a reliable ratio. This is also important for further confirmatory testing that may follow initial screening. Table 3 shows non-interfering antihypertensives that may be used during the workup to control blood pressure.[5] As adjusting the antihypertensive regimen can be a lengthy process and is not without risks, it should only be pursued for patients expected to benefit from the diagnosis and treatment of primary aldosteronism. A discussion with a physician with a special interest in

Fig. **Effects of interfering drugs on aldosterone and renin**



ARR aldosterone:renin ratio

Table 2 **Factors that may lead to false-positive or false-negative aldosterone:renin ratio results**

Factor	Effect on aldosterone plasma concentration	Effect on renin concentration	Effect on aldosterone:renin ratio
Drugs*			
Beta adrenergic blockers	↓	↓ ↓	↑ (FP)
Central agonists (e.g. clonidine, alpha methyldopa)	↓	↓ ↓	↑ (FP)
Non-steroidal anti-inflammatory drugs	↓	↓ ↓	↑ (FP)
Potassium wasting diuretics	→ ↑	↑ ↑	↑ (FN)
Potassium sparing diuretics	↑	↑ ↑	↓ (FN)
ACE inhibitors	↓	↑ ↑	↓ (FN)
Angiotensin receptor antagonist	↓	↑ ↑	↓ (FN)
Calcium channel blockers (dihydropyridines)	→ ↓	↑	↓ (FN)
Renin inhibitors	↓	↓ ↑	↑ (FP) ↓ (FN)
Potassium status			
Hypokalaemia	↓	→ ↑	↓ (FN)
Potassium loading	↑	→ ↓	↑
Dietary sodium			
Sodium restriction	↑	↑ ↑	↑ (FN)
Sodium loading	↓	↓ ↓	↑ (FP)
Advancing age	↓	↓ ↓	↑ (FP)
Premenopausal women (vs males) †	→ ↑	↓	↑ (FP)
Other conditions			
Renal impairment	→	↓	↑ (FP)
PHA-2	→	↓	↑ (FP)
Pregnancy	↑	↑ ↑	↓ (FN)
Renovascular hypertension	↑	↑ ↑	↓ (FN)
Malignant hypertension	↑	↑ ↑	↓ (FN)

FN false negative FP false positive

↓ decreases effect ↑ increases effect → has no effect

PHA-2 pseudohypoaldosteronism type 2 (familial hypertension and hyperkalaemia with normal glomerular filtration rate)

* Renin inhibitors lower plasma renin activity, but raise direct renin concentration. This would be expected to result in false-positive aldosterone:renin ratios for renin measured as plasma renin activity and false negatives for renin measured as direct renin concentration.

† In premenopausal, ovulating women, plasma aldosterone concentrations measured during the menses or the proliferative phase of the menstrual cycle are similar to those of men but rise briskly in the luteal phase. Because renin concentrations are lower, the aldosterone:renin ratio is higher than in men for all phases of the cycle, but especially during the luteal phase during which aldosterone rises to a greater extent than renin. False positives can occur during the luteal phase, but only if renin is measured as direct renin concentration and not plasma renin activity. In preliminary studies, some investigations have found false positives on the current cut-offs for women in the luteal phase. Accordingly, it would seem sensible to screen women at risk in the follicular phase, if practicable.

Source: adapted from reference 3

Table 3 **Drugs that do not interfere with calculating the aldosterone:renin ratio**[5]

	Starting dose	Maximum dose
Sustained-release verapamil*	180 mg daily	240 mg daily
Moxonidine	200 micrograms once at night	200 micrograms twice daily after two weeks
Prazosin	0.5 mg twice daily	5 mg three times a day
Hydralazine hydrochloride	12.5 mg twice daily	50 mg three times a day

* Administration of verapamil as two divided doses may provide better coverage over 24 hours, if necessary. Doses higher than 240 mg daily may be used, but are often limited by adverse effects, therefore addition of a second drug is advised before increasing the verapamil dose.

hypertension should be considered, and the patient should understand why changes to their treatment are being proposed.

When adjusting the antihypertensive regimen, drugs are usually ceased one at a time at a rate of one per week, or more slowly if there is a need to maintain blood pressure control. Diuretics including spironolactone are stopped first, as they require a washout of at least four weeks. Other antihypertensives need to be ceased for a minimum of two weeks before testing.[3] Blood pressure should be monitored at least twice a week. Home blood pressure monitoring can be helpful for selected patients. Non-interfering antihypertensives, if required, may be introduced and up-titrated one at a time. The target blood pressure may be individualised based on the patient's previous blood pressure, their age and the duration of hypertension. This blood pressure may be higher than the usual target for the prevention of cardiovascular disease, given that these drug substitutions are only temporary.

Patients should be informed of the symptoms of a hypertensive emergency, what a safe blood pressure is and how to seek medical attention if their blood pressure exceeds this. Provide counselling about the adverse effects, the frequency of dosing for the non-interfering antihypertensives, and the precautions for driving.

Conclusion

Identifying secondary hypertension presents an opportunity to modify a patient's cardiovascular risk profile beyond what is achievable by antihypertensive therapy alone. Renal disease and primary aldosteronism are common causes.

A methodical approach to identifying the cause is necessary and must take into account the drugs being used by the patient. Advice on test selection and patient preparation to optimise the value of initial investigations can be provided by a chemical pathologist or hypertension specialist. Patients who have abnormal results will require further investigations to confirm the cause. <

Conflicts of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. Most patients who have primary aldosteronism also have hypokalaemia.

4. A high aldosterone:renin ratio in a patient taking an ACE inhibitor suggests primary aldosteronism.

Answers on page 177

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FURTHER READING

Gabb G. What is hypertension? Aust Prescr 2020;43:108-9. https://doi.org/10.18773/austprescr.2020.025

NEW DRUGS

New drugs

Aust Prescr 2021;44:170–1
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First published 1 September 2021

Cariprazine hydrochloride

Approved indication: schizophrenia

Reagila (Gedeon Richter)

1.5 mg, 3 mg, 4.5 mg and 6 mg capsules

Antipsychotic drugs are part of the multifaceted management of schizophrenia. Since the emergence of the 'second generation' antipsychotics, these drugs, such as aripiprazole and risperidone, have become first-line therapy. Cariprazine hydrochloride adds to the available options.

The effect of cariprazine is thought to be due to its action on dopamine and serotonin (5-HT) receptors. It is a partial agonist at dopamine D_2 and D_3 and $5HT_{1A}$ receptors, with preferential binding to the D_3 receptor. Cariprazine is an antagonist at $5\text{-}HT_2$ and histamine H_1 receptors.

Treatment begins with a dose of 1.5 mg once daily. This can be increased gradually to 6 mg daily depending on the patient's response. Doses are well absorbed and, apart from grapefruit juice, cariprazine can be given with or without food. The drug is extensively metabolised. This metabolism involves cytochrome P450 3A4 and co-administration of enzyme inhibitors, such as diltiazem, erythromycin and ketoconazole, or inducers, such as St John's wort and rifampicin, is contraindicated. Cariprazine is also not recommended for patients with severe hepatic or renal impairment. Most of the metabolites are excreted in the faeces. While the effective half-life of cariprazine is about two days, one of its active metabolites has a half-life of eight days. When cariprazine treatment ends it can take up to a month for all the drug and its metabolites to be excreted. Women planning a pregnancy should be advised to avoid conception for at least 10 weeks after stopping treatment. (Cariprazine has had adverse effects in studies of pregnant animals.) The long half-life also means that there may be a delayed response to changes in the dose of cariprazine.

A proof-of-concept trial was carried out in adults with acute exacerbations of previously diagnosed schizophrenia. In this six-week trial 392 patients were randomised to receive daily doses of cariprazine 1.5–4.5 mg (128), 6–12 mg (134) or a placebo (130). Efficacy was assessed with the Positive and Negative Syndrome Scale (PANSS). At the start of the study the average PANSS score was approximately 95. This reduced by 9.74 points with placebo, 14.53 points with lower dose cariprazine and 12.62 points with higher dose cariprazine. Only the lower dose range was statistically superior to placebo.[1]

Most of the phase III trials used the lower doses of cariprazine. A pooled analysis of three trials in acute exacerbations of schizophrenia included 1024 patients who took cariprazine and 442 who took placebo. Their mean baseline PANSS score was approximately 97. After six weeks this was reduced by 16.8 points with a daily dose of cariprazine 1.5 mg and by 19.5 points with a 6 mg dose. The mean reduction in the placebo groups was 10.3 points.[2] One trial used aripiprazole and another used risperidone as active controls. These drugs had effects on the PANSS score that were similar to those of cariprazine.

While the biggest effect of cariprazine was on positive symptoms, such as delusions, it also reduced negative symptoms, such as a blunted affect. A phase III trial therefore specifically studied the effect of cariprazine in 460 adults with predominantly negative symptoms. These patients had had schizophrenia for an average of 12–13 years. On a rating scale for negative symptoms (PANSS–FSNS) they had an average score of approximately 27.5. The patients were randomly switched from their usual treatment to either cariprazine or risperidone. Over 26 weeks, both drugs reduced the PANSS score and the 230 patients who took cariprazine had a bigger reduction on the scale of negative symptoms (8.9 vs 7.44 points). The mean daily doses used were cariprazine 4.2 mg and risperidone 3.8 mg.[3]

As schizophrenia is a long-term illness, cariprazine has been studied for the prevention of relapse. Patients were stabilised on open-label cariprazine for 12 weeks then randomly allocated to take cariprazine or a placebo. This double-blind phase was for 26–72 weeks with the mean duration of treatment being 257 days in the 101 patients who took cariprazine. A relapse occurred in 24.8% of these patients compared with 47.5% of the 99 patients in the placebo group. The median time to relapse was 296 days in the placebo group, but could not be calculated for the cariprazine group.[4]

The adverse effects of cariprazine resemble those of other antipsychotic drugs. They include akathisia, extrapyramidal symptoms and tremor. Compared to placebo more patients taking cariprazine experience insomnia, restlessness and weight gain. Cariprazine can affect blood pressure, but appears to have little

The new drug commentaries in *Australian Prescriber* are prepared by the Editorial Executive Committee. Some of the views expressed 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.

effect on the QT interval of the ECG. Caution is advised in patients at risk of stroke. Measurement of lipids and liver function is recommended, but cariprazine does not appear to cause hyperprolactinaemia. In animal studies, cariprazine has been associated with cataracts and changes in the retina. It is unknown if the same effects will be seen in humans.

Cariprazine may have a higher affinity for D_3 receptors than D_2 receptors, but it is unclear if this has any clinically relevant effects. While cariprazine has improved the negative symptoms of schizophrenia, the difference between cariprazine and risperidone on the PANSS–FSNS scale was 1.46 points. This was statistically significant, but may not be a clinically significant advantage.[3] In the short-term trials the effect of cariprazine seemed similar to the effects of aripiprazole and risperidone. When deciding which drug to prescribe for controlling acute schizophrenia, it may be a consideration that cariprazine takes five days to reach 90% of its steady-state concentration. Patients with schizophrenia may move from the oral form of an antipsychotic drug to its depot formulation, however there is no long-acting injectable depot formulation of cariprazine.

TT manufacturer provided additional useful information

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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.

NEW DRUGS

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First published 6 September 2021

Related articles:
BNT162b2 vaccine for prevention of COVID-19
ChAdOx1-S vaccine for prevention of COVID-19

Elasomeran

Approved indication: prevention of COVID-19

Spikevax (Moderna)
5 mL multidose vials containing 0.2 mg/mL

Elasomeran is the fourth COVID-19 vaccine to be given provisional approval in Australia. It is indicated to prevent COVID-19 in individuals 12 years old and over.

Like the BNT162b2 COVID-19 vaccine (made by Pfizer), elasomeran is a messenger RNA (mRNA-1273) vaccine. The RNA encodes for a modified form of the spike protein of the coronavirus. It is encapsulated in lipid nanoparticles to enable the RNA to be taken into cells after intramuscular injection. The cells produce the spike protein which then induces an immune response which includes neutralising antibodies.

Preliminary investigations,[1] including some patients over the age of 56 years,[2] established the dose regimen to be used in a randomised phase III trial.[3] This was two doses of 100 micrograms of mRNA (0.5 mL) given 28 days apart.

The ongoing phase III trial in the USA has reported its results for people followed up for a median of 63 days after the second injection.[3] The per-protocol analysis included 14,134 adults who received the two doses of the vaccine and 14,073 who received a saline placebo. Efficacy was assessed by the occurrence of symptomatic COVID-19 at least 14 days after the second injection. Eleven cases occurred in the vaccine group compared to 185 cases in the placebo group. This gives a vaccine efficacy of 94.1% for the prevention of symptomatic infection. The efficacy was similar across all age groups. Elasomeran had an efficacy of 100% against severe infection as the 30 cases that had severe COVID-19, including one death, were all in the placebo group.

Adverse reactions at the injection site were more frequent with the vaccine than with placebo (88.6% vs 18.8% after the second injection).[3] These effects included pain, tenderness, erythema and induration and may have a delayed onset. There have been cases of anaphylaxis, so people need to be observed after vaccination. More common adverse reactions include fatigue, headache, myalgia and arthralgia. The frequency and severity of these adverse effects was greater after the second dose of vaccine. They persist for an average of three days. Myocarditis and pericarditis may be rare adverse effects.

Elasomeran has to be stored between –25 °C and –15 °C. Thawed vials should be stored at 2 °C to 8 °C until used. Each multidose vial contains enough vaccine for 10 doses (0.5 mL). Dilution is not required. The deltoid muscle is the preferred site for injection.

Like all the vaccines against COVID-19, the efficacy and safety data for elasomeran are incomplete. For example, children and pregnant women were not included in the phase III trial and there was a limited number of immunocompromised patients.[3] The efficacy against different viral strains and the duration of protection is unknown. A small study suggests that elasomeran produces higher antibody concentrations than the BNT162b2 vaccine in people over 50 years old.[4]

[X] manufacturer did not respond to request for data

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Recombinant varicella zoster virus glycoprotein E antigen vaccine

Aust Prescr 2021;44:173–4
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First published 11 August 2021

Approved indication: prevention of herpes zoster and postherpetic neuralgia

Shingrix (GlaxoSmithKline)
single-dose vials containing powder for reconstitution

Herpes zoster (shingles) is a painful condition characterised by a unilateral vesicular rash with a dermatomal distribution. The number of blisters and the area of affected skin vary, as does the severity of associated symptoms and complications, such as muscle weakness and postherpetic neuralgia. Herpes zoster may occur in anyone who has previously had varicella zoster infection (chickenpox) as it is caused by reactivation of the latent varicella zoster virus from a dorsal nerve root ganglion. Such reactivation is more likely in older age or during immunosuppression which results in lowered zoster-specific cell-mediated immunity. While herpes zoster resolves in most people without sequelae, some have persistent and significant discomfort. Postherpetic neuralgia, which is more common in people over 50 years old, is characterised by debilitating pain and dysaesthesia for more than three months.

The first vaccine against herpes zoster became available in Australia in 2006. Ten years later, this live attenuated vaccine was offered through the National Immunisation Program to people aged 70–79 years. It has a moderate protective efficacy of 51% in adults 60 years of age or older. However, as a live vaccine, it cannot be administered to immunocompromised patients.[1]

This new vaccine is a recombinant form of the herpes zoster glycoprotein E antigen, also known as Hz/su. It does not contain live virus and therefore may be suitable for immunocompromised patients pending the results of further studies. The US Centers for Disease Control and Prevention advises that the vaccine can be administered to people on low-dose immunosuppressive therapy.[2] Glycoprotein E has a central role in herpes zoster infection and is an important target for immune responses. The vaccine is designed to induce antigen-specific cellular and humoral immune responses in persons with pre-existing immunity against herpes zoster virus. However, it is not necessary to have a documented history or serological evidence of prior varicella infection.[2] Vaccination involves two 0.5 mL intramuscular injections, preferably in the deltoid muscle, with a two-to-six-month interval between doses.

A placebo-controlled phase III trial, ZOE-50, involved 15,411 participants, aged 50 years or older with no history of zoster infection or vaccination. There were 7698 people who were randomised to receive the vaccine and 7713 who received injections of placebo. The second dose was given two months after the first. After a mean follow-up of 3.2 years, herpes zoster was diagnosed in six people in the vaccine group and 210 in the placebo group.[3]

A parallel trial, ZOE-70, randomised 14,816 adults 70 years of age or older. Among the people who could be evaluated after 3.7 years of follow-up, herpes zoster occurred in 23 of the 6541 vaccine recipients and in 223 out of the 6622 placebo recipients.[4]

In pooled data from both trials for participants age 70 years and older, the vaccine efficacy was 91.3%.[4] Pooled data from all participants 50 years and older showed that the incidence of postherpetic neuralgia was 0.1 per 1000 person-years in the vaccine group and 0.9 in the placebo group, indicating a vaccine efficacy of 91.2%.[4] The efficacy in preventing postherpetic neuralgia is most likely due to the vaccine reducing the rate of herpes zoster, because there was no reduction in the incidence of postherpetic neuralgia in the small number of vaccinated people who did develop herpes zoster.

In ZOE-70 a randomly selected subgroup of 1025 participants recorded adverse events within seven days of vaccination. Injection-site reactions were reported in 74.1% of vaccine recipients and 9.9% of those who received placebo. The most common local reactions to the vaccine were pain (68.7%), redness (39.2%) and swelling (22.6%). These symptoms typically lasted less than four days. General symptoms included myalgia (31.2%) and fatigue (32.9%). In the mean follow-up period of four years, the incidence of serious adverse events was similar in the vaccine (16.6%) and placebo (17.5%) groups. Potential immune-mediated diseases occurred in 1.3% and 1.4%.[4]

The vaccine may be given at the same time as seasonal influenza vaccine, but at a different site. There are no data in relation to concomitant injection with other vaccines.

The recombinant herpes zoster glycoprotein E vaccine appears to be of higher efficacy than the live vaccine.[1] However, the incidence of injection-site reactions is higher than with live vaccine (74.1%[4] vs 48%[5]). The live vaccine protects for about five years, but its efficacy declines from 63.9% in the 60–69-year-old group to 37.6% in those aged 70 years or over with respect to protecting against herpes zoster. In contrast, in

ZOE-50 and ZOE-70, the efficacy of the recombinant vaccine did not appear to decline with increasing age. It was similar in all age groups (50–59, 60–69, and 70 years and over).[4] However, if herpes zoster does occur after vaccination with the live vaccine, its efficacy against postherpetic neuralgia (66.5%) does not decline with age.[6] The recombinant vaccine has evidence of maintaining its effectiveness for four years, but studies are required to explore its longer term efficacy.

Since 2020, when the live vaccine was discontinued in the USA, the recombinant vaccine has been the only vaccine available.[2] The Australian approval is for people aged 50 years or older.

[X] manufacturer did not respond to request for data

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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.

Sotrovimab

Approved indication: COVID-19

Xevudy (GlaxoSmithKline)
vials containing 500 mg/8mL concentrate for dilution

While vaccines are essential for controlling the pandemic caused by SARS-CoV-2, there is a need to identify the best treatment for patients who become infected and develop COVID-19. Sotrovimab is a monoclonal antibody that has been given provisional approval for patients, over 12 years of age, who do not require oxygen therapy, but have an increased risk of hospitalisation or death.

Sotrovimab has been genetically engineered to bind to the spike protein of SARS-CoV-2. Animal studies show that this binding neutralises the virus. The genetic engineering extends the half-life of the monoclonal antibody. This gives sotrovimab a median elimination half-life of about 49 days. The recommended regimen is therefore a single intravenous infusion of 500 mg. Sotrovimab must be diluted before being infused over 30 minutes.

When sotrovimab was provisionally approved the results of a clinical trial (COMET-ICE) had not been published in a peer-reviewed journal. This trial randomised unvaccinated patients with confirmed infection who were at high risk of complications. Risk factors included asthma, chronic obstructive pulmonary disease, chronic kidney disease and diabetes. An interim analysis reported that COVID-19 had progressed in 3/291 patients infused with sotrovimab and 21/292 given a placebo. The five patients who subsequently needed intensive care were all from the placebo group.[1]

The data considered by the Therapeutic Goods Administration included 528 patients given sotrovimab and 529 given placebo. Approximately 20% of these patients were over 65 years old. The infusion was given within five days of the onset of symptoms. A large difference emerged between the two groups and the trial stopped recruiting new patients. By day 29, 6% of the patients in the placebo group had died or been admitted to hospital compared with 1% of the sotrovimab group. Two people in the placebo group died.

During the trial the rate of adverse events was similar for sotrovimab and placebo (22% vs 23%). Common complaints were diarrhoea, nausea and headache. Infusing an antibody also has the potential to cause hypersensitivity reactions.

Due to its rapid approval, the data on sotrovimab are limited. Further research will be needed to know if it is effective for young children, pregnant women or the immunosuppressed. The effect of vaccination on the safety and efficacy of sotrovimab is also unknown. It is uncertain which at-risk patients should be given sotrovimab. Approximately 16 people need to be treated to prevent one hospitalisation or death, so the logistics of giving everyone at risk an infusion may exceed the available resources and the supply of the drug. There is also the concern that antiviral resistance could develop.

T manufacturer provided the AusPAR

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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.

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NEW DRUGS

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First published 11 August 2021

Trabectedin

Approved indication: soft tissue sarcoma

Yondelis (Specialised Therapeutics) vials containing 0.25 mg or 1 mg powder for reconstitution

Soft tissue sarcomas are rare cancers that have a poor prognosis with up to 50% of patients developing metastases. Chemotherapy is not very effective, so the median survival with metastatic disease is about one year. The search for new treatments has led to the study of trabectedin. This is an alkaloid that was originally extracted from a sea squirt (*Ecteinascidia turbinata*). The molecule can now be synthesised.

Trabectedin is thought to act by binding to DNA. This distorts the DNA, which affects transcription and DNA repair mechanisms. These changes lead to multiple effects including cytotoxic, antiproliferative and antiangiogenic actions.

The drug has to be infused over 24 hours every three weeks. Trabectedin is widely distributed after infusion. It is metabolised by cytochrome P450 3A4 so plasma concentrations are likely to be altered by inducers and inhibitors of this enzyme system. Trabectedin is also a substrate of P-glycoprotein, so it may interact with drugs such as verapamil. Most of the metabolites are excreted in the faeces. The terminal half-life is about 180 hours. Liver impairment will increase concentrations of trabectedin. Renal impairment is unlikely to have much effect as little drug is excreted in the urine, but there have been no studies in patients with severe impairment.

The main clinical trial of trabectedin enrolled patients with unresectable, locally advanced or metastatic leiomyosarcoma or liposarcoma. These patients had previously been treated with at least an anthracycline regimen. A group of 345 patients was randomised to receive trabectedin and 173 were randomised to receive dacarbazine. They were treated every 21 days until the disease progressed or toxicity became unacceptable. An interim analysis took place after 188 patients had died. This found that there had been an objective response in 9.9% of the patients given trabectedin and 6.9% of those given dacarbazine. Progression-free survival was 4.2 months with trabectedin and 1.5 months with dacarbazine, but there was little difference in median overall survival (12.4 vs 12.9 months).[1]

The trial continued with eventually 384 patients in the trabectedin group and 193 in the dacarbazine group. In the final analysis 67% of the trabectedin group had died compared with 64% of the dacarbazine group. The median overall survival was 13.7 months with trabectedin and 13.1 months with dacarbazine.[2]

Trabectedin is a very toxic drug. Nearly all patients will experience adverse effects and in 63% of cases these will be serious. Approximately 4% of the patients had a fatal adverse reaction to trabectedin. In the clinical trial, dose reductions were required in 42% of the patients and 63% required a delay in treatment. The corresponding figures for dacarbazine were 12% and 42%.[2] Reasons for revising the trabectedin regimen include neutropenia, thrombocytopenia and increases in bilirubin or liver enzymes. Treatment must stop if the patient develops rhabdomyolysis, cardiomyopathy, or capillary leak syndrome. There can be severe injection-site reactions with tissue necrosis if there is extravasation of trabectedin. It is therefore strongly recommended that the drug is infused through a central venous line. Patients should be given intravenous dexamethasone half an hour before the infusion. This may provide some protection for the liver as well as reducing the nausea and vomiting associated with trabectedin.

Despite the significant hepatic and haematological toxicity, patients were able to endure trabectedin for longer than dacarbazine. The median number of treatment cycles was four versus two for dacarbazine.[2] There was no difference in overall survival between the drugs, but switching patients from dacarbazine to other drugs may have affected this result. The median time to starting another therapy was 3.5 months in the dacarbazine group and 6.8 months with trabectedin. However, a post hoc analysis taking these factors into account did not show a great advantage for trabectedin.[2] In Australia its use will be limited to patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have already been treated with a regimen containing an anthracycline.

T T manufacturer provided additional useful information

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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.

A:

ANSWERS TO SELF-TEST QUESTIONS

1 True
2 False
3 False
4 True

Corrections

Management of insomnia in primary care [Correction]

Aust Prescr 2021;44:177
First published 10 August 2021
https://doi.org/10.18773/austprescr.2021.043

The article on management of insomnia in primary care (Aust Prescr 2021;44:124-8) has been corrected. View corrected article.

In the drug management paragraph on melatonin, the treatment duration should have been over a 'three-week period' rather than a 13-week period: "Melatonin (2 mg extended-release formulation) is effective in treating insomnia in adults over the age of 55 over a three-week period."

The ocular adverse effects of oral drugs [Correction]

Aust Prescr 2021;44;177
First published 13 August 2021
https://doi.org/10.18773/austprescr.2021.045

The article on adverse effects of oral drugs on the eye (Aust Prescr 2021;44:129-36) has been corrected. View corrected article.

Table 1, showing common or serious ocular adverse effects of selected oral drugs, incorrectly listed dutasteride and finasteride as alpha$_1$ adrenergic receptor antagonists (row 1). These drugs have now been removed from the table.

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