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ARTICLE

Treating osteoporosis: risks and management

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SUMMARY

Osteoporosis, osteopenia and minimal trauma fractures are becoming increasingly common in the ageing population. Fractures cause increases in morbidity and mortality and have a significant financial impact on the healthcare system and society.

Addressing risk factors for osteoporosis early may prevent or delay the onset of fractures and use of drugs. Calcium and vitamin D supplementation may benefit people with a high risk of deficiency (e.g. institutionalised older people) but may not be required in people without risk factors. Impact and resistance exercises and physical activity can increase bone density and prevent falls.

Antiresorptive drugs such as bisphosphonates and denosumab remain first-line treatment options for osteoporosis. The ongoing need for bisphosphonates should be assessed after five years and treatment may then be interrupted in some patients. Progressive bone loss will recur slowly. Denosumab therapy should not be interrupted without switching to another therapy, as post-treatment bone loss can progress rapidly. All patients will need ongoing monitoring and most will require some long-term therapy once started.

Raloxifene may be considered in women who do not tolerate first-line antiresorptive drugs. Romosozumab is a new anabolic treatment for osteoporosis and, together with teriparatide, is subsidised as second-line therapy for individuals with severe disease and multiple fractures. Specialist referral should be considered for patients who sustain fractures while undergoing osteoporosis therapy.

Introduction

Osteoporosis is a common musculoskeletal disease in older people characterised by a progressive loss in bone mineral density and microarchitectural deterioration. In Australians aged over 50 years, 40–60% of women and 25–30% of men will experience a minimal trauma fracture in their lifetime.[1] Fractures cause pain, disability and a reduced quality of life,[2] and are associated with an increased re-fracture rate. Fractures lead to a five-year mortality rate of 25%, which increases to up to 50% in the event of a re-fracture.[3] The population-attributable mortality risk associated with fractures in Australians aged 45 years and over has been found to be similar to that associated with cardiovascular diseases and diabetes, highlighting the need to identify and treat osteoporosis.[4]

Osteoporosis is a silent disease before a fracture occurs, so the exact prevalence is hard to determine. Even after diagnosis, it is often undertreated, with approximately 25% of Australian patients with osteoporosis having no history of receiving osteoporosis medicines.[5]

Osteoporosis risk assessment

There are a number of non-modifiable and modifiable risk factors, diseases and drugs associated with osteoporosis and minimal trauma fractures. The fracture risk for an individual can be accurately predicted using the Garvan Fracture Risk or FRAX calculators.[6,7] Age, a family history of hip fractures and previous fractures are key risk factors. All men and women over the age of 50 years who have sustained a fracture have a higher risk of subsequent fractures and should be assessed and considered for treatment. Bone mineral density testing is also recommended and subsidised for all men and women over 70 years of age. Along with falls-risk screening, it is recommended as part of general health checks for all individuals, yet medical record audits indicate that this prevention strategy is currently underused.[8]

Osteoporosis can be defined using bone mineral density testing, which generates a T-score and Z-score. The T-score reflects the number of deviations from the peak bone mass of age-, sex- and ethnicity-matched norms. A T-score less than –2.5 indicates a significant reduction in bone mass. The Z-score reflects the number of standard deviations from the average bone mass of age-, sex- and ethnicity-matched norms. A Z-score less than –2.0 should prompt a more complete search for secondary causes of osteoporosis.

Management strategies

Addressing lifestyle risk factors, appropriately treating predisposing conditions and minimising the unnecessary prescription of drugs associated with osteoporosis may slow the decline in bone

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density and prevent minimal trauma fractures. Some modifiable risk factors are summarised in the Box.[9] Various management strategies can help decrease the risk of osteoporosis or delay its onset.

Exercise

Exercise throughout a person's lifetime can delay the onset of osteoporosis. Exercise in children and adolescents is strongly associated with a higher peak bone density in adulthood. This effect is seen most with high-impact exercises such as hopping, skipping and jumping.[10] Even an increase in leisurely physical activity can cause a durable increase in bone mass that can persist into early old age.[11] In older people, low-impact exercises such as walking and swimming may slow the decline in bone mass, whereas higher impact exercises, resistance exercises, and combinations of different types of exercises may increase bone density.[12-15]

The frequency and severity of falls may also be reduced by exercise programs, such as Stay On Your Feet and Stepping On. The main benefits are seen with programs focused on balance and function, or programs that involve multiple types of exercise (e.g. balance exercise plus resistance exercise).[16] Where possible, individuals are encouraged to perform a combination of weight-bearing, resistance and balance exercises. Information regarding the types of exercises that can be recommended is available from the Healthy Bones Australia fact sheets.

Calcium

Adequate calcium concentrations are crucial to prevent bone loss and fractures. The recommended dietary intake of calcium is 1000–1300 mg per day, depending on age and sex. Common calcium-rich foods include dairy products, chickpeas, beans, sardines and tofu. A dietary calcium calculator is available on the International Osteoporosis Foundation website.

Most older Australians do not achieve the recommended dietary intake of calcium. Along with information and guidance on dietary modifications, daily supplements of 500–600 mg are sometimes needed for these people. Calcium supplementation, particularly with vitamin D, can reduce the rate of bone loss and fractures in people who are deficient in calcium such as frail elderly people.[17]

There is conflicting evidence regarding oral calcium supplementation and the risk of major adverse cardiac events, which include myocardial infarction and stroke. Recent meta-analyses on cardiovascular disease risk have revealed a range from a 10% relative risk reduction to a 15% relative risk increase.[18-20]

Vitamin D

Vitamin D is important for the absorption and use of calcium in the body. Evidence suggests about a third of Australians have vitamin D deficiency.[21] While small amounts of vitamin D are absorbed through food, most is received from direct sunlight. Those with fair skin require 6–7 minutes of mid-morning or mid-afternoon sun exposure outdoors during the summer and up to 30 minutes during the winter to maintain adequate concentrations of vitamin D. People with darker skin will require 3–6 times the length of exposure. Additionally, window glass, full-coverage clothing and sunscreen inhibit the transmission of ultraviolet B radiation and thus vitamin D synthesis in the skin. Vitamin D synthesis is also less efficient in older people.[22] Improving vitamin D concentrations reduces the risks of falls and fractures in older people,[23,24] particularly when combined with adequate calcium concentrations.[17,25]

Box **Factors associated with osteoporosis and minimal trauma fractures**[9]

Lifestyle	Conditions	Drugs
Increased falls risk	Endocrine diseases	Glucocorticoids
• poor balance	Sex hormone deficiency	Excessive thyroid hormone replacement
• vision impairment	Cushing syndrome	Androgen deprivation therapy
Sarcopaenia	Hyperthyroidism	Aromatase inhibitors
Smoking	Hyperparathyroidism	Proton pump inhibitors
Alcohol consumption	Diabetes mellitus	Thiazolidinediones
Physical inactivity	Impaired gastric absorption	Selective serotonin reuptake inhibitors
Low calcium intake	Coeliac disease	Long-term heparin
Vitamin D deficiency	Upper gastrointestinal surgery	Antiepileptics
Low protein intake	Rheumatoid arthritis	Cyclophosphamide
		Sedating drugs
		Antihypertensives

Routine vitamin D supplementation for primary prophylaxis is not recommended for community-dwelling adults.[26] Those who have risk factors or symptoms of vitamin D deficiency should have their vitamin D concentrations measured. These are ideally measured in late winter or early spring, when serum 25-hydroxyvitamin D concentrations are the lowest. Optimal mineral metabolism, bone density and muscle function are achieved when serum 25-hydroxyvitamin D concentrations are greater than 50 nanomol/L. If testing is carried out in late summer, the concentration should be 10–20 nanomol/L higher.

Patients with vitamin D deficiency should start supplementation (Table 1). Routine vitamin D and calcium supplementation reduces the risks of falls and fractures in people with established osteoporosis or institutionalised people.[17] There are very few adverse effects related to oral vitamin D supplementation. When combined with calcium, there is a small risk of hypercalcaemia, nephrolithiasis and gastrointestinal symptoms.

Drugs for osteoporosis

Pharmacotherapy is indicated for individuals with a significantly increased risk of fractures. First-line treatment is available under the Pharmaceutical Benefits Scheme (PBS) for:

- those 50 years of age and over who have sustained a minimal trauma fracture
- those 70 years of age and over with established osteoporosis
- those who require long-term corticosteroids (minimum three months) on at least 7.5 mg of prednisolone or equivalent per day.

Antiresorptive therapy can reduce the risk of fractures by up to 50%. There is a consensus to treat individuals who have a hip fracture risk of more than 3% or any fracture risk of more than 20% over 10 years.[9] However, treatment for this indication alone is not subsidised under the PBS. There should be a shared discussion taking a patient's fracture risk, preferences and costs into consideration, although many drugs such as bisphosphonates are inexpensive.

Before starting drugs for osteoporosis, ensure that all patients have adequate vitamin D and calcium concentrations and that any secondary causes for osteoporosis have been managed. Table 2 summarises the common and notable rare adverse effects of different osteoporosis treatments.

Bisphosphonates

Bisphosphonates inhibit osteoclast activation and prevent bone resorption. They slow the rate of bone loss, improve bone mineral density and reduce both hip and vertebral fractures. Alendronate, risedronate and zoledronic acid are currently available for osteoporosis in Australia. Head-to-head evidence for bisphosphonates is lacking. At the time of publication, bisphosphonates are cheaper than other drug treatments.

Oral and intravenous bisphosphonates are contraindicated in patients with renal impairment and should be avoided if the estimated glomerular filtration rate is less than 35 mL/minute/1.73 m^2.[27]

Safety data are robust for the use of oral bisphosphonates up to five years and intravenous bisphosphonates up to three years.[28] The fracture risk should then be re-assessed, and most specialists normally extend treatment if the patients fall under any of the following high-risk categories:

- femoral neck T-score less than –2.5
- femoral neck T-score less than –2.0 with vertebral fractures
- a recent fracture.

Oral and intravenous bisphosphonates can be extended up to 10 and six years, respectively, without an increase in adverse events compared to placebo.[28-34] Treatment extension in these high-risk populations has been shown to be effective in preventing new vertebral fractures, but minimally beneficial for preventing hip fractures. Patients at lower risk have not been shown to experience more clinical fractures

Table 1 **Initial treatment of vitamin D deficiency**

Vitamin D status	25-hydroxyvitamin D concentration (at the end of winter)	Recommended vitamin D supplementation*	Follow-up
Mild deficiency	30–49 nanomol/L	1000–2000 IU per day	3–5 months after starting supplementation; annually recommended if receiving treatment for osteoporosis
Moderate deficiency	12.5–29 nanomol/L	3000–5000 IU per day (for 6–12 weeks) followed by a maintenance dose of 1000–2000 IU per day	
Severe deficiency	<12.5 nanomol/L		

* Alternatively, higher doses may be given less frequently when needed.

Table 2 **Adverse effects of osteoporosis drugs**

Drug	Common adverse events	Notable rare adverse events
Oral bisphosphonates	Hypocalcaemia Upper gastrointestinal effects (gastro-oesophageal reflux, erosive oesophagitis)	Osteonecrosis of the jaw* Atypical femoral fractures†
Intravenous bisphosphonates	Hypocalcaemia Flu-like illness following infusion	Osteonecrosis of the jaw* Atypical femoral fractures†
Denosumab	Hypocalcaemia Injection-site reactions Atraumatic vertebral fractures following discontinuation	Osteonecrosis of the jaw* Atypical femoral fractures†
Raloxifene	Hot flushes Venous thromboembolism	Stroke
Teriparatide	Hypercalcaemia Injection-site reactions	Theoretical risk of osteosarcoma
Romosozumab	Injection-site reactions	Possible increased risk of major adverse cardiovascular events (myocardial infarction, stroke) Osteonecrosis of the jaw* (few case reports) Atypical femoral fractures† (few case reports)

* Risk factors include dental extractions, implants, poorly fitting dentures, pre-existing dental disease, glucocorticoid use and smoking.
† Risk factors include rheumatoid arthritis, increased femoral bowing, thicker lateral cortices at the femoral shaft and Asian ethnicity.

after stopping therapy due to the durable effects of bisphosphonates.[28-34] If therapy is stopped, the fracture risk is generally re-assessed in 2–3 years or upon re-fracture to consider restarting therapy.

Oral bisphosphonates

Alendronate and risedronate are inexpensive and have once-weekly or once-monthly oral dosing. It is important to counsel patients to take oral bisphosphonates in the morning on an empty stomach with a full glass of water and to remain upright for 30 minutes after ingestion to ensure adequate drug absorption and prevent erosive oesophagitis. The main limitations of oral bisphosphonates are their upper gastrointestinal effects. Dysphagia, achalasia or an inability to remain upright for 30 minutes after tablet ingestion are absolute contraindications. They should also be used with caution in patients who have previously undergone upper gastrointestinal or bariatric surgery, as this may impair drug absorption and increase the risk of adverse events.

Intravenous bisphosphonates

Zoledronic acid is an intravenous bisphosphonate given as an annual infusion. It can help overcome the gastrointestinal limitations of oral formulations, but it has other potential adverse effects, most notably the risk of flu-like reactions following infusions. Myalgias and arthralgias can also occur and may be prolonged. Patients with renal impairment can be at greater risk of these reactions, and in such cases, the infusion rate could be reduced. Alternatively, a different class of drug that is not affected by renal function, such as denosumab, should be considered. There is also a small risk of atrial fibrillation and uveitis with intravenous zoledronate. Bisphosphonates have been associated with the rare and serious adverse events of atypical femoral fractures and osteonecrosis of the jaw.

Denosumab

Denosumab is a monoclonal antibody that reversibly inhibits bone resorption by reducing osteoclast formation and differentiation while increasing osteoclast apoptosis. It increases bone mineral density at the lumbar spine and hip and reduces the risk of fractures. Denosumab is administered as a six-monthly subcutaneous injection. In contrast to bisphosphonates, denosumab can be used in patients with chronic kidney disease. However, these patients are particularly at risk of hypocalcaemia, so baseline concentrations of calcium and vitamin D should be assessed before starting therapy.

Patients should either continue denosumab indefinitely or be transitioned to an alternative treatment drug (e.g. bisphosphonates) for at least 12 months on discontinuation. Unlike bisphosphonates, the effect of denosumab is not durable and is rapidly reversible

after cessation.[35] Stopping denosumab or missing doses is associated with an increased risk of atraumatic vertebral fractures.[35-39] The incidence of these fractures has been reported to be between 7% and 10%, with more patients sustaining multiple vertebral fractures compared to patients who have not received denosumab.[35-38] These rebound effects can be seen as early as seven months after the previous dose and can persist for two years following discontinuation.[38,39]

Bisphosphonates such as alendronate and zoledronic acid appear to be effective in minimising the bone loss and mitigating the increased fracture rate associated with denosumab discontinuation.[35,38,39] Between 2012 and 2017, over 80% of Australian patients receiving denosumab did not receive subsequent bisphosphonate treatment following cessation.[5] This number should decrease with increased awareness of the adverse effects of stopping denosumab. Denosumab has also been associated with the rare and serious adverse events of atypical femoral fractures and osteonecrosis of the jaw.

Raloxifene

Raloxifene is a selective oestrogen receptor modulator that reduces postmenopausal bone loss. It reduces the risk of vertebral fractures, but it does not reduce the risk of non-vertebral fractures. It is taken as a daily tablet, which patients may find inconvenient. Raloxifene is an alternative to bisphosphonates or denosumab (if they cannot be tolerated) for women with postmenopausal osteoporosis and may be appropriate for younger women with spinal osteoporosis soon after menopause. It increases the incidence of hot flushes, which can be a significant problem in young postmenopausal women. Raloxifene reduces the risk of breast cancer, so it can be considered in women with a high risk of breast cancer. However, it increases the risk of deep venous thrombosis, and other evidence suggests slightly increased mortality after stroke.[40]

Menopausal hormone therapy

Menopausal hormone therapy can consist of combined oral or transdermal oestrogen with oral progesterone therapy, or tibolone alone as a daily tablet. It is an effective option for women who require treatment for osteoporosis and have either premature menopause or significant postmenopausal symptoms requiring pharmacotherapy. Menopausal hormone therapy reduces the risk of all fractures, while tibolone has not been shown to reduce the risk of hip fractures.[41] While menopausal hormone therapy may be useful when osteoporosis and fracture prevention therapy is required in women younger than 50 years of age, the risks of this therapy must be considered with long-term use.[41,42]

Teriparatide

Teriparatide is a synthetic form of parathyroid hormone that stimulates bone formation. It is given as a once-daily subcutaneous injection. Teriparatide is used to treat severe osteoporosis and is subsidised for an 18-month treatment course in Australia when patients continue to sustain fractures and remain severely osteoporotic (T-score less than –2.5) despite receiving at least 12 months of first-line treatment. The rate of vertebral fractures may be reduced by up to 65%. Teriparatide has been shown to reduce non-vertebral and hip fractures by up to 55%.[43,44]

Contraindications include age younger than 25 years, known or suspected Paget's disease, previous radiotherapy to the bone and pre-existing hypercalcaemia, malignancy, kidney disease and primary hyperparathyroidism. Following the treatment course, patients should receive antiresorptive therapy (e.g. a bisphosphonate, denosumab, raloxifene) to maintain the improvements in bone density and the fracture risk reduction effect. Without this, the anabolic effects of these drugs are lost.

Romosozumab

Romosozumab is an antisclerostin monoclonal antibody that decreases bone resorption and increases bone formation. Similar to teriparatide, it is only subsidised in patients with severe osteoporosis who continue to sustain fractures despite receiving at least 12 months of first-line treatment. It is administered as two subcutaneous injections once a month for 12 months.

Romosozumab is superior to both alendronate and teriparatide in improving bone density at the spine and hip. It has been shown to reduce the relative risk of vertebral fractures by 73% compared to placebo, and by 48% compared to weekly alendronate. It has also been shown to reduce the risk of non-vertebral fractures by 19% and hip fractures by 38%.[45,46]

The ARCH trial demonstrated a small increase in the incidence of cardiovascular events in the romosozumab arm, which was not seen in other trials.[47] More supporting data are required, but romosozumab is currently not recommended for patients with a high risk of myocardial infarction or stroke. Other common adverse effects include injection-site reactions. Romosozumab should not be used for more than 12 months given the lack of long-term safety data. Following the treatment course, patients should receive antiresorptive therapy (e.g. a bisphosphonate, denosumab, raloxifene) to maintain the improvements in bone density and the fracture risk reduction effect. Without this, the anabolic effects of these drugs are lost.

Sequential treatment with first-line anabolics

There is evidence to suggest that the treatment sequence may be important in managing osteoporosis. The response to anabolic drugs such as romosozumab may be blunted by previous treatment with antiresorptive drugs. Some studies have shown superior and durable gains in bone density when anabolic drugs are given before antiresorptive drugs. More research is required to determine if the gains in bone density also correlate with a reduced fracture risk in these patients.[47] Given this evidence, for some treatment-naïve patients who present with severe osteoporosis (T-score less than –3.0) following a fracture, the option of first-line treatment with an anabolic drug such as romosozumab should be discussed with the patient. However, this is not a PBS-listed indication.

Monitoring osteoporosis

Repeat bone mineral density testing with dual-energy X-ray absorptiometry is useful to monitor a patient's response to therapy. It is recommended to test patients one year after starting or changing therapy, which can be spaced out to every 2–3 years if the bone density remains stable.[48] Annual testing is recommended in patients with accelerated bone loss, such as in patients using glucocorticoids.[48] It is important that serial bone density measurements are obtained using the same machine where possible as there can be significant variability between different models and clinics.

Bone turnover markers

Bone turnover markers may be useful in monitoring osteoporosis in some patients. The main bone turnover markers used in Australia are procollagen type 1 N-terminal propetide, which is a marker of bone formation, and C-terminal collagen telopeptide (CTX), which is a marker of bone resorption. Measuring the concentrations of these markers may be useful if there are concerns regarding reduced oral absorption due to previous surgery, a poor drug administration technique (e.g. taking oral bisphosphonates too close to mealtimes) or poor medication adherence.[49] As such, CTX testing is available once annually under the Medicare Benefits Schedule.

Conclusion

With our ageing population, the individual and economic impacts of osteoporosis will continue to rise. A combination of lifestyle and pharmacological strategies should be used to prevent fractures in older people, with effective screening tests available to identify those at higher risk. All men and women over the age of 50 years who sustain a fracture, and all those over 70 years of age regardless of whether they have sustained a fracture, should be assessed for antiresorptive therapy. Tailored impact and resistance exercises are safe and effective for preventing falls and can improve bone density.

Therapy can and should be tailored to each patient's preference for the mode of delivery and adverse-effect profile. Weekly (alendronate, risedronate) or monthly (risedronate) oral treatments and annual intravenous (zoledronate) or six-monthly subcutaneous injections (denosumab) are the preferred first-line treatments because of their ability to reduce the risk of vertebral and hip fractures. Other treatments are available for patients who cannot use or fail to respond to first-line treatment and continue to sustain fractures (raloxifene, teriparatide, romosozumab). Surveillance for potential adverse effects and the need to continue therapy is essential. <

Conflicts of interest: none declared

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LETTERS

Letters to the Editor

Role of empagliflozin in chronic lithium toxicity

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Regarding the Medicinal Mishap 'Chronic lithium toxicity', I wonder if the role that empagliflozin played in the patient's cascade of symptoms was considered.[1] Acidosis can occur in the setting of reduced oral intake or hypovolaemia. Interestingly, a case report[2] suggests that lithium concentrations may be reduced in patients taking empagliflozin, although there is no mention of this in the product information for empagliflozin.

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Ian Whyte and Frank Reimann, the authors of the article, comment:

Thank you for your question about the role empagliflozin may have played in our patient's cascade of symptoms.

While the patient's diarrhoea and neurological findings could not be related to empagliflozin, the biochemical abnormalities were consistent with euglycaemic ketoacidosis.[1] Empagliflozin can produce this complication in the presence of physiological stress.[2] However, the patient's blood ketone concentrations were only mildly raised, and the large anion gap was better explained by renal failure. Further, the abnormalities had normalised by 48 hours without administration of insulin or glucose solutions.

The case report highlights a potential role of empagliflozin in facilitating lithium excretion.[3] Although sodium-glucose co-transporter 2 (SGLT2) inhibitors can acutely increase lithium renal clearance by decreasing proximal sodium reabsorption, the effect is transient and, within a month, compensated for by a rise in plasma renin activity and aldosterone.[4] This makes it unlikely that the patient's long-term empagliflozin was affecting his lithium clearance. Additionally, for SGLT2 inhibitors to exert an effect on the renal tubule, sufficient kidney function would have been required.

In the context of acute illness and severe kidney injury, most of the patient's regular medicines could have caused mishaps and required sick-day plans.

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ARTICLE

Erectile dysfunction: causes, assessment and management options

SUMMARY

Erectile dysfunction is one of the most common male sexual dysfunctions. The diagnosis can usually be made by a detailed history and examination.

Men with erectile dysfunction benefit from multimodal management strategies. These include lifestyle modification, medical treatment and psychosexual counselling and therapy.

An oral phosphodiesterase-5 inhibitor is often prescribed for erectile dysfunction. Providing simple and clear instructions is critical to realise the full benefits of these drugs.

Those with severe vascular disease or a history of pelvic surgery may not respond to phosphodiesterase-5 inhibitors. Anxiety or unrealistic expectations can also result in a poor response.

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Keywords
erectile dysfunction, impotence, phosphodiesterase-5 inhibitors

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Introduction

Erectile dysfunction is a prevalent sexual dysfunction in men.[1] Male sexual dysfunction can occur at any age, but erectile dysfunction and diminished libido increase with age. There may be underlying causes.

Multimodal management is needed, but when drugs are indicated, oral phosphodiesterase-5 inhibitors or self-injectables such as alprostadil are options for erectile dysfunction.

It is important to initially discuss treatment objectives and outcomes, and set realistic expectations to avoid dissatisfaction. While there is information available about drugs to use in erectile dysfunction, the information is rarely accompanied with specific advice for the patient on timing and other details about how to use the drugs.

Erectile dysfunction

Men with erectile dysfunction are unable to achieve an erection firm enough for sexual intercourse.

Causes

There are many causes and risk factors for erectile dysfunction (Box 1).[2] These were traditionally classified as organic, psychogenic or mixed. However, with advancements in the fields of psychological science and sexual medicine, the current view is that the aetiological factors are multimodal[3] – biological, psychological, sociocultural, relational and sexual.

Assessment

Men presenting with erectile dysfunction are initially assessed with a comprehensive history (Box 1). This helps the clinician to understand and differentiate the causes as predisposing (why this person?), precipitating (why now?) and perpetuating (what is keeping the problem?) factors. The history includes lifestyle (quality and quantity of sleep, snoring and sleep apnoea, weight, exercise, alcohol, smoking history), general health (physical and mental, medicines) and a relationship and psychosexual history.[4,5] Box 2 shows some key questions to ask. Eliciting details about the quality of morning erections and erectile capacity during other sexual activities (e.g. masturbation) are critical to understand the underlying aetiology.[4] The history of past and current treatment for erectile dysfunction, and the response achieved, helps in tailoring further management.

A distinction must be made whether the man has erectile dysfunction or premature ejaculation because some men are not good at describing their problem. The man with premature ejaculation may say he has erectile dysfunction because he loses his erection early after ejaculation. Conversely, the man with erectile dysfunction may complain of premature ejaculation as he rushes to ejaculate quickly before he loses his erection. Erectile dysfunction and premature ejaculation are often confused but can occur together.

The history should include a review of medicines (as listed in Box 1). This could provide valuable insight about the sexual adverse effects of certain drugs and, more importantly, a timeline between starting a specific drug and the onset of erectile complaints.

The physical examination should include, at a minimum, general parameters (weight, waist circumference, body mass index and blood pressure) and the genitals. If investigations are indicated, the

Box 1 Risk factors for erectile dysfunction

- Advanced age
- Atherosclerosis-related risk factors (e.g. cardiovascular disease, cigarette smoking, hypertension, dyslipidaemia, diabetes mellitus)
- Pelvic surgery (e.g. radical prostatectomy), radiation, trauma
- Endocrinological conditions (e.g. hypogonadism, hyperprolactinaemia, thyroid disorder)
- Obesity and metabolic syndrome
- Substance abuse – alcohol, illicit drugs (e.g. cannabis, barbiturates, cocaine, heroin, methamphetamine)
- Psychological (partner-related, stress, guilt, situational anxiety, self-image problems, low self-esteem, history of sexual abuse, highly restricted sexual upbringing, generalised anxiety disorder, depression, psychosis)
- Erectile dysfunction associated with other sexual dysfunction(s) (e.g. premature ejaculation, sexual aversion disorder, anorgasmia)
- Medicines:
  - antihypertensives (e.g. diuretics, alpha and beta blockers)
  - psychotropics (e.g. selective serotonin reuptake inhibitors and other antidepressants, antipsychotics, anxiolytics)
  - anticonvulsants, anti-Parkinson's drugs
  - hormone-affecting drugs – antiandrogens, corticosteroids, chronic opioid use
- Neurological conditions (Alzheimer's disease, multiple sclerosis, Parkinson's disease, stroke), spinal cord and peripheral nerve disorders (diabetic neuropathy)
- Penile abnormalities (e.g. Peyronie's disease, venous leak)

Box 2 Key questions in the assessment of erectile dysfunction

- Is the problem intermittent, global or situational?
- Is the problem recent or long term?
- Is there an unusual curvature of the erection or an episode of sexual trauma to the erect penis?
- Has the patient ever suffered from mental health problems?

minimum is serum lipids, fasting glucose or ideally glycated haemoglobin.[4,5] Should hypogonadism be suspected, measure serum testosterone on a blood sample taken before 11 am.[4]

A validated questionnaire, for example the International Index of Sexual Function (IIEF-5),[6] can be an adjunct to history and examination. However, such questionnaires should not be used alone for diagnosing erectile dysfunction.[5]

Management options

The initial treatment of erectile dysfunction addresses lifestyle changes and psychological or relationship problems. Sex therapy is indicated particularly when there is a significant psychological contribution to erectile dysfunction and when there is no response to medical management.[7] Ideally, sex therapists should be healthcare professionals with specific qualifications in the field of human sexuality along with skills in counselling and psychosexual therapy. General practitioners, psychologists and sexual health physicians can offer certain aspects of sex therapy, whereas a well-qualified and trained sex therapist can offer comprehensive psychosexual education, counselling and therapy.

Phosphodiesterase-5 inhibitors

The first step of drug treatment is an oral phosphodiesterase-5 inhibitor:

- sildenafil 25, 50 and 100 mg
- vardenafil 5 and 20 mg
- avanafil 50, 100 and 200 mg
- tadalafil 5, 10 and 20 mg.

Phosphodiesterase-5 inhibitors work best if taken 1–2 hours before sexual intercourse. Tadalafil has a two-hour lead-in time, when taken as required, so is often used as a daily low-dose (5 mg) treatment. Daily dosing may also benefit men with erectile dysfunction who have benign prostatic hyperplasia as it can improve lower urinary tract symptoms.

Large meals and alcohol should be avoided before a dose, but when phosphodiesterase-5 inhibitors are taken daily, food and alcohol have less impact on the response. It is critical to educate patients that phosphodiesterase-5 inhibitors do not create sexual stimuli. They only help with getting and maintaining an erection when there is adequate external sexual stimulation.

Depending on the severity of erectile dysfunction, the clinician decides on the appropriate starting dose. Importantly, patients should be made aware that they need to take the drug as prescribed and, on five to six occasions, to assess the treatment effect. Failure to provide this information could lead to a suboptimal or no response, which in turn could lead to an inappropriate use of higher doses or the addition of other treatment options. The response to phosphodiesterase-5 inhibitors can be affected by anxiety, alcohol, excessive expectations of how these drugs should work, and not waiting long enough for them to work. The American Urological Association Guideline states that sildenafil, tadalafil, vardenafil and avanafil have similar efficacy in men with erectile dysfunction and that dose-response effects across phosphodiesterase-5 inhibitors are small and non-linear.[8] While there is no firm evidence that switching from one phosphodiesterase-5 inhibitor to another will have a beneficial effect, it is worth a clinical attempt provided the expectations are discussed with the patient.

The classic adverse effects of phosphodiesterase-5 inhibitors are flushed face, headaches, blocked nose, altered colour vision (mainly with sildenafil) and

gastric reflux. Most of these adverse effects have a dose-response pattern. The average rates are similar across the phosphodiesterase-5 inhibitors except for dyspepsia (lowest rates reported with avanafil), flushing (lowest rates reported with tadalafil), and myalgia (lowest rates reported with vardenafil and avanafil).[8] Tadalafil is associated with low back and leg pain which often go away when the drug is stopped.

Phosphodiesterase-5 inhibitors should not be prescribed if the patient is taking nitrates or uses 'recreational' amyl nitrite. There is a risk of a precipitous blood pressure drop.

Injectable drugs

Penile injections tend to be used when oral phosphodiesterase-5 inhibitors are not effective. The drugs used for intracavernosal penile injection are vasoactive. They include alprostadil, which may be combined with papaverine and phentolamine. Penile injections work rapidly so sexual activity may begin within 10–15 minutes of injecting.

Care must be taken to use the lowest effective dose to avoid priapism which can be a medical emergency. The patient may also experience delayed post-injection pain. Patient education (by means of explaining or referring to product information, or video demonstrations) is very important. The drug needs to be injected into the shaft at 10 o'clock or 2 o'clock positions, altered between different attempts, avoiding obvious veins and fibrosis.

Devices

High rates of patient satisfaction have been reported for vacuum erection devices. They can be an effective and low-cost treatment option for any men with erectile dysfunction but more so for those with diabetes, spinal cord injury or after prostatectomy.[8] Older men may tend to use vacuum mechanical devices as they are drug free. However, vacuum erection devices can be cumbersome and require some training in correct use.

Shockwave therapy applies acoustic shock waves to the penis. This aims to improve vascularisation. Shockwave therapy appears to work best for the older patient with vasculogenic erectile dysfunction, but lacks robust evidence of efficacy.[9]

A penile implant is a restorative treatment option. It is a very effective treatment no matter the aetiology or severity of the erectile dysfunction and even if all other treatments have failed or are not suitable. However, it is irreversible.

Evaluation of treatment outcomes

Evaluating treatment outcomes for erectile dysfunction depends on the management goals that were established before treatment. Erectile capacity across different sexual activities (intercourse, masturbation), quality of morning erections, reduction in distress and overall sexual satisfaction are some of the measures used to assess progress.

Conclusion

Erectile dysfunction is a common male sexual dysfunction. It requires a comprehensive clinical assessment and multimodal management. This may involve GPs, specialists and allied health professionals trained in the field of sexology.

Conflicts of interest: none declared

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ARTICLE

Bariatric surgery and medicines: from first principles to practice

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bariatric surgery, malabsorption syndromes, obesity, pharmacokinetics

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SUMMARY

Obesity is a major public health issue with significant health and financial costs. Almost one in three Australian adults are living with obesity.

Bariatric surgery can have a role in the management of obesity. There is evidence for its effectiveness in preventing or reversing chronic health conditions.

The type of bariatric surgery can significantly impact the absorption, distribution, metabolism or elimination of orally administered drugs. Some changes can be predicted from pharmacokinetic and physiological effects, but management should be individualised.

The effect of weight loss itself after bariatric surgery may require drug doses to be altered.

A review of the patient's medicines and ongoing follow-up are important before and after surgery to ensure optimal outcomes.

Introduction

Two-thirds of all Australian adults are either overweight (36%) or obese (31%) and the proportion of adults living with obesity is continuing to rise.[1] In 2019 Australia had the sixth highest proportion of overweight or obese people over 15 years old among 22 member countries of the Organisation for Economic Co-operation and Development.[2] During 2015, overweight and obesity contributed to 8.4% of the total burden of disease and was the leading risk factor contributing to non-fatal burden.[2]

Given the high disease burden from obesity, bariatric surgery is now more frequently being considered as an effective option for sustaining weight loss in patients with this progressive chronic health condition.[2-4] When less invasive methods for weight loss have failed, indications for bariatric surgery according to National Health and Medical Research Council criteria are Class III obesity (body mass index (BMI) ≥40 kg/m^2) or a BMI of at least 35 kg/m^2 with obesity-related comorbidities.[5] From 2005–06 to 2014–15, the total number of weight loss operations more than doubled, from about 9300 to 22,700.[1] It is now estimated that over 97,000 procedures are being undertaken each year in Australia.[6] Given the lifelong follow-up required, GPs will be managing increasing numbers of patients who have had bariatric surgery. This includes considering the effects of surgery on the drugs the patient is taking.

Bariatric operations

Bariatric surgery is the most effective treatment modality for patients living with obesity. It often results in a significant and sustainable loss of 20–35% of the starting weight.[7]

To manage the implications of bariatric surgery, it is important to understand the different types of operations (see Fig.). Bariatric surgeries are classified as having restrictive or malabsorptive properties, or a combination of both. Restrictive surgeries reduce the volume of food that can be consumed at one time, leading to a reduced total caloric intake. Malabsorptive procedures create a diversion around substantial portions of the digestive tract causing reduced absorption of food and drugs.

In Australia, sleeve gastrectomy is currently the most common bariatric operation, followed by gastric bypass surgery (encompassing Roux-en-Y gastric bypass and one anastomosis gastric bypass). Sleeve gastrectomy is primarily restrictive while both Roux-en-Y and one anastomosis gastric bypass combine restriction with malabsorption.[8]

Laparoscopic adjustable gastric banding is now being performed much less frequently. It is purely a restrictive procedure and problems with drug therapy generally only occur if the band is too tight or a complication has occurred such as band slippage. In these situations it is crucial that the patient is reviewed at a bariatric clinic.

Effect on pharmacokinetics

Despite the number of bariatric surgeries performed, the effects on drugs remain poorly understood and documented. Bariatric surgery can significantly impact the absorption, distribution, metabolism or elimination of orally administered drugs through changes

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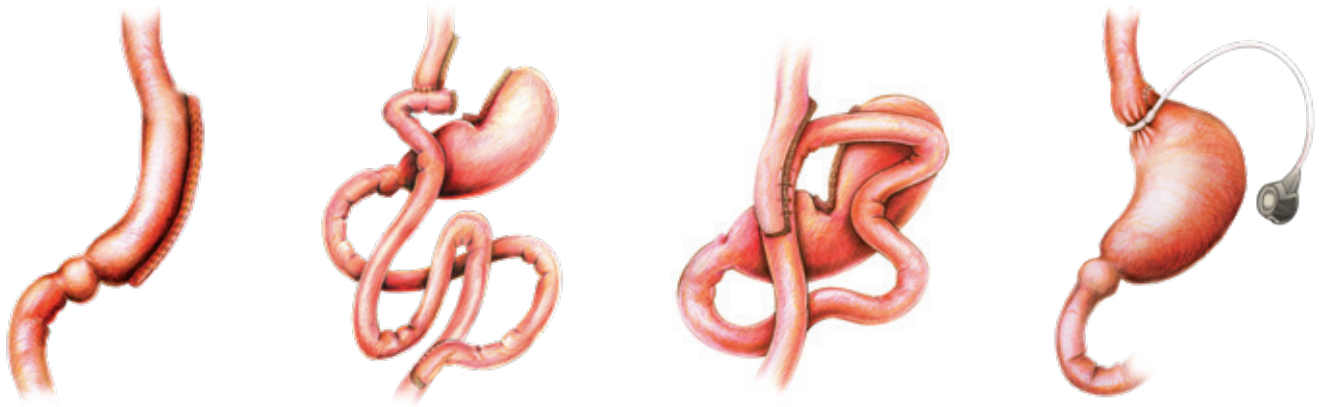
to the anatomy, body weight and adipose tissue composition. Factors that affect the bioavailability of drugs depend on the type of bariatric surgery. These factors include decreased absorptive surface area, reduced exposure to metabolising enzymes and drug transporters in the gut, the rate of gastric emptying and an increased intragastric pH.[9-12]

Patients undergoing bariatric surgery often have comorbidities requiring multiple drugs. Pharmacotherapy may be complicated not only by physiological or pharmacokinetic changes in absorption and metabolism following surgery, but also by subsequent improvement in weight-related chronic health conditions.

Effect on drug management

By anticipating expected changes to the pharmacokinetics of specific drugs and physiological changes due to the type of surgery, there are general approaches to medicine management that can be implemented (see Box).[10,13] Strategies to improve drug absorption are not required for all patients and the clinical significance of altered absorption, bioavailability and elimination requires individual assessment, monitoring and close follow-up.[10,11] There are large inter- and intra-individual variations and the doses of drugs for many chronic conditions may need to be modified as weight loss occurs. Common chronic conditions that may improve with weight

Fig. **Common procedures in bariatric surgery**



Sleeve gastrectomy | **Roux-en-Y gastric bypass** | **One anastomosis gastric bypass** | **Laparascopic adjustable gastric banding**

Illustrations supplied by Medtronic

Box **General principles for managing drugs after bariatric surgery**[10,13]

- Review the patient's medicines regularly.
- Monitor for decreased efficacy. If efficacy is decreased, consider dose increase, change in formulation or route, or alternative drugs for same indication.
- Monitor for adverse effects and signs of toxicity, which may be a possible result of increased bioavailability.
- Drugs for chronic conditions may need dose reductions, or to be stopped, as obesity-related health conditions improve.
- Be cautious with drugs with a narrow therapeutic index. These will require close monitoring and titration especially following gastric bypass. When possible, monitor serum concentrations and the effects of these drugs e.g. anticoagulants, anticonvulsants, lithium, digoxin.
- Consider staggering the doses of drugs, particularly liquid formulations, due to the reduced capacity of the stomach. Use higher concentration liquid formulations to reduce the volume of each dose.
- Avoid larger tablets (over 10 mm) as they can become stuck and add to the tablet burden. Crush or use alternative formulations.
- Avoid enteric-coated or sustained-release formulations. These products can pass through the altered gastrointestinal tract before absorption is complete and, for some preparations, there is a risk that the inert formulation matrix could accumulate.
- Avoid effervescent formulations.
- Avoid drugs that potentially damage gut mucosa e.g. non-steroidal anti-inflammatory drugs, aspirin and bisphosphonates.
- After gastric bypass, avoid products (including over-the-counter products) that contain a large amount of sucrose, corn syrup, lactose, maltose, fructose, honey or mannitol, as they can result in dumping syndrome.
- Be aware of drugs that may contribute to weight gain.

Table **Effects of bariatric surgery on commonly prescribed drugs**

Drugs	Potential effects of bariatric surgery	Comments/management
Antihypertensives	Doses will often need to be reduced or stopped quite soon after surgery, and sometimes even in the preoperative (VLED) phase.	Monitor blood pressure and enquire about symptoms of postural hypotension. Continued surveillance of blood pressure is needed after surgery because of the high risk of recurrence over time. Beware of diuretics and dehydration in the early postoperative phase.
Drugs for diabetes	Requirements for insulin and other antidiabetic drugs change rapidly in the preoperative (VLED) and early postoperative phase.	Monitor blood glucose and adjust doses on a case-by-case basis. Care with insulin or antidiabetic drugs that increase the risk of hypoglycaemia (e.g. sulphonylureas) Metformin to be changed to immediate-release preparation.
Lipid-modifying	Overall, the effects of weight loss on lipids are variable and incomplete.	Monitor lipids and absolute cardiovascular risk. Adjust doses on a case-by-case basis.
Antidepressants (e.g. SSRIs, SNRIs, tricyclics)	Small studies suggest that the bioavailability of antidepressants may be reduced after gastric bypass, particularly in the first six months after surgery. Serum concentrations of SSRIs returned to baseline in 50% of cases after 12 months in one small study, suggesting adaptation to effects may occur over time. In a significant portion of patients, depression may improve as a result of weight loss.	Monitor patients closely for signs of withdrawal or reduced efficacy. Doses may need to be increased or may require a change in formulation (e.g. to immediate release or liquid), particularly in the first six months following bypass surgery.
Antipsychotics/ mood stabilisers	There may be impaired absorption of antipsychotics. Lithium concentrations are influenced by the volume of distribution and may become toxic after bariatric surgery.	Monitor for decreased efficacy or signs of toxicity and adjust the dose accordingly.
Thyroxine	Absorption of thyroxine may be reduced after bariatric surgery, however weight loss may result in improvement of hypothyroidism (and hence a decrease in dose). Observational studies suggest most patients will need either no change or a reduction in thyroxine doses. In some patients (particularly those with autoimmune thyroiditis), thyroxine dose requirements may increase.	Periodically monitor thyroid function and adjust doses on a case-by-case basis. There is no need for preventive adjustment of thyroxine doses.
Analgesics	Reduction in absorption of opioids and slow-release analgesic preparations. Less need for analgesia with ongoing weight loss.	Monitor for opioid withdrawal. Monitor for improvement in painful conditions. Immediate-release or non-oral preparations are preferable. Avoid non-steroidal anti-inflammatory drugs.

SNRI serotonin and noradrenaline reuptake inhibitor
SSRI selective serotonin reuptake inhibitor
VLED very low energy diet
Source: adapted with permission from reference 14

loss include hypertension, diabetes and pain from osteoarthritis (see Table).[14]

Frequent reviews of medicine management tailored to the individual patient and treatment targets are required. Regular communication between the patient's bariatric clinic, their usual GP and any relevant treating specialists is crucial with regards to any medicine changes. Pharmacists play an important role,[11,12] contributing as a member of the clinical team through the provision of a range of services including comprehensive medication reviews, which are very useful both in preparation for bariatric surgery and postoperatively.

Alcohol

The effect of alcohol may increase following surgery due to altered alcohol metabolism. Gastric bypass surgery is associated with:

- accelerated alcohol absorption
- higher maximum alcohol concentration
- longer time to eliminate alcohol
- increased risk of alcohol use disorder.

The increased risk of alcohol misuse after surgery could be due to addiction transference. Alcohol (or other substances) may be substituted for food as a coping mechanism.[15-17]

Contraception

Oral contraceptives may not be reliable after bariatric surgery. This is due to lower absorption and bioavailability after gastric bypass and concerns about effectiveness following all types of bariatric surgery.[4,9] Alternative contraceptive methods should be considered, in particular long-acting reversible contraception.

It is important that women avoid pregnancy for at least 12–18 months following bariatric surgery. Fertility can improve dramatically after weight loss, especially in women with polycystic ovary syndrome, therefore effective contraception becomes even more important.[3,4]

Nutrition

Following bariatric surgery, lifelong vitamin and mineral supplements are required, tailored to each patient's needs. These may include multivitamins, calcium, vitamin D, iron and vitamin B_{12}. Routine supplementation does not ensure an absolute prevention of deficiencies over time, mainly because of individual variations in micronutrient absorption, nutritional requirements, the type of bariatric surgery and adherence to therapy. Periodic laboratory surveillance for nutritional deficiencies is recommended and supplementation should be individualised accordingly.[4] Given all this, it is crucial that a bariatric-trained dietitian is part of the management team.

Conclusion

Bariatric surgery may alter the pharmacokinetics of orally administered drugs because of physiological and anatomical changes to the gastrointestinal tract, reduced body weight and altered adipose tissue composition. The impact on drugs depends on the type of bariatric surgery. There is limited evidence to guide practice in an area where GPs will be increasingly required to have some knowledge and practical skill. A multidisciplinary approach with regular review of medicines and close monitoring is required. <

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ARTICLE

Drug management of autosomal dominant polycystic kidney disease

SUMMARY

Autosomal dominant polycystic kidney disease is the most common genetic kidney disease affecting adults. Approximately 60% of patients develop kidney failure by 60 years of age due to slowly expanding kidney cysts.

A healthy lifestyle and rigorous control of blood pressure slow kidney cyst growth. These interventions can be effective in reducing progression to kidney failure and cardiovascular disease, especially if started in early adulthood.

Tolvaptan, a vasopressin receptor antagonist, slows kidney cyst growth and the decline in the estimated glomerular filtration rate by 1 mL/minute/1.73 m^2 per year. It is indicated in patients with chronic kidney disease who are at high risk of progression to kidney failure.

Chronic kidney pain is common and can be managed with analgesics, and input from pain specialists if refractory.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of Stage 5 chronic kidney disease (kidney failure) in adults, accounting for 6.4% of Australians receiving chronic dialysis or undergoing transplantation. It is a single-gene disorder due to germline variants in either the PKD1 or PKD2 gene, estimated to be carried by 25,000 Australians. The main clinical manifestation is the formation of hundreds of microscopic fluid-filled kidney cysts during childhood that grow slowly. Sixty per cent of patients develop massive kidney enlargement, chronic pain, hypertension, cardiovascular disease and kidney failure, as well as other extrarenal manifestations, by the sixth decade of life (see Box). The diagnosis of ADPKD is typically made in young adults with a positive family history who have multiple kidney cysts detected on a kidney ultrasound performed for screening (see Box). Genetic testing is only required to assist with family planning or if there is diagnostic uncertainty.

Stage 5 chronic kidney disease is the main cause of disability and death in patients with ADPKD and is usually preceded by a progressive decline in the estimated glomerular filtration rate (eGFR) by approximately 2.5 mL/minute/1.73 m^2 per year between the second and fourth decades of life. Encouraging young adults with ADPKD to engage in their health during the early asymptomatic period provides the best opportunity to significantly delay the onset of kidney failure and prevent cardiovascular disease. In particular, there is good evidence that lifestyle modifications (smoking cessation, weight reduction, aiming for a body mass index less than 25 kg/m^2, reduction in dietary sodium intake to 80–100 mmol/day and regular physical activity) slow kidney cyst growth and the decline in kidney function. Providing education via PKD Australia fact sheets and genetic counselling are also recommended.

Blood pressure control to slow disease progression

Hypertension is a key complication that should be identified during early adulthood. It develops in most adults and up to 20% of children.[1] Hypertension occurs due to intrarenal activation of the renin–angiotensin–aldosterone system secondary to the

Box Typical hallmarks of autosomal dominant polycystic kidney disease

- Young asymptomatic adult with a family history of autosomal dominant polycystic kidney disease
- Multiple, bilateral kidney cysts on ultrasound – meeting the Pei–Ravine unified ultrasound criteria[2]
- Progressive symptomatic complications in approximately 60% with ageing (kidney pain, chronic kidney disease, hypertension or kidney failure)
- Variable extrarenal complications: aneurysms (intracranial 6–20%; aortic 5%), extrarenal cysts (hepatic >90%, 5% symptomatic), diverticular disease (40%), abdominal hernias (inguinal, incisional or para-umbilical 45%) and depression (up to 60%)
- Elevated risk of premature cardiovascular disease (50%) due to hypertension, chronic kidney disease or cardiac valvular abnormalities

growth of multiple kidney cysts and endothelial dysfunction. In young adults, biannual screening of blood pressure by a healthcare provider or at home using a validated monitor is one possible approach to screening for hypertension. Early detection and treatment of hypertension have significant benefits, as they prevent left ventricular hypertrophy, reduce albuminuria and slow kidney cyst growth.

The treatment of hypertension follows standard guidelines and should be integrated with routine screening for other cardiovascular disease risk factors (such as hyperlipidaemia and impaired glucose tolerance).[2] The first-line drug classes for treating hypertension are blockers of the renin–angiotensin–aldosterone system (either ACE inhibitors or angiotensin receptor antagonists).[2] The choice of second-line drugs is tailored to specific patient circumstances. Contrary to historical opinion, the addition of thiazide diuretics or calcium channel blockers is not contraindicated as second-line drugs and they can be used in combination with angiotensin blockers.[2,3]

In patients with early-stage disease (eGFR >60 mL/min/1.73 m^2), the recommended blood pressure target is between 120/70 mmHg and 130/80 mmHg. In patients who can tolerate lower blood pressures without significant lightheadedness, a target of 110/75 mmHg can be specified.[2] For such lower targets, home monitoring using a validated instrument is a good method for monitoring blood pressure. In patients with advanced disease (eGFR 25–60 mL/min/1.73 m^2), a blood pressure target of 120/70 mmHg to 130/80 mmHg is appropriate.[2]

Disease-modifying drugs to slow disease progression

Arginine vasopressin augments the postnatal growth of kidney cysts. Tolvaptan is a specific oral vasopressin type 2 receptor antagonist and is indicated in patients with ADPKD at high risk of developing kidney failure (see Pharmaceutical Benefits Scheme reimbursement criteria, Tables 1–2). The regulatory approval was based on the results of two large phase III multicentre randomised controlled trials (TEMPO 3:4 and REPRISE), which showed that tolvaptan reduced the annual decline in the eGFR by approximately 1 mL/minute/1.73 m^2 compared to placebo (Table 3).[4-6]

The main adverse effect of tolvaptan is massive aquaresis (mean urine volume of 5–7 L/day) due to the off-target suppression of vasopressin-mediated water reabsorption in the collecting duct. This occurs in all patients and requires behavioural adaptation to increase daily fluid intake. At least 23% of patients eventually discontinue tolvaptan due to the impact on daily life. About 5% of patients develop reversible idiosyncratic hepatic toxicity, so monitoring of liver function is essential. It should be performed before starting treatment, monthly for the first 18 months and then three-monthly lifelong while continuing to receive tolvaptan. Maintaining adequate hydration also reduces vasopressin, but high-quality evidence indicates that drinking more than 2–2.5 L of water a day does not slow disease progression in patients with ADPKD.[6]

Pharmacological management of flank, abdominal or back pain

Flank, abdominal or back pain is experienced by 60% of patients with ADPKD before the age of 40 years. Acute and severe nociceptive flank, abdominal or back pain usually signifies an acute kidney event:

- the rupture of a kidney cyst, which is often associated with macroscopic haematuria
- a bacterial urinary tract or kidney cyst infection
- renal colic due to a kidney stone.

Appropriate investigations (imaging, midstream specimen of urine for microscopy and culture) can be used to easily diagnose these problems. In contrast, chronic flank, abdominal or back pain is complex (consisting of nociceptive, neuropathic and nociplastic

Table 1 **Pharmaceutical Benefits Scheme (PBS) reimbursement criteria and indications for tolvaptan in patients with autosomal dominant polycystic kidney disease**

Criteria	Specified requirements as per the PBS
Practitioner	Must be treated by a nephrologist
Kidney function	Must have an eGFR 30–89 mL/min/1.73 m^2 at the time of starting drug treatment
Historical evidence of rapidly progressing kidney disease	Must have an eGFR decline of either >5 mL/min/1.73 m^2 in 1 year OR >2.5 mL/min/1.73 m^2/year over 5 years

eGFR estimated glomerular filtration rate

Table 2 **Prescribing considerations for tolvaptan for autosomal dominant polycystic kidney disease**

Category	Prescribing considerations
Indication	To slow the progression of cyst development and renal insufficiency in adults with ADPKD and CKD Stages 1–3 with rapidly progressing disease
Targets and mechanism of action	Selective vasopressin V_2 receptor antagonist, which reduces the reabsorption of water in the collecting duct and promotes free water diuresis. Metabolised by the CYP3A4 system
Contraindications	Elevated liver enzymes, liver injury, volume depletion, anuria, hypernatraemia, poor thirst regulation, hypersensitivity to constituents, pregnancy and breastfeeding
Limiting factors and precautions	Severe liver injury, potent aquaresis, hypernatraemia, hyperkalaemia, dehydration and hyperglycaemia
Drug interactions	CYP3A inhibitors and inducers (e.g. grapefruit juice, clarithromycin, ketoconazole, rifampicin, phenytoin, carbamazepine), P-glycoprotein inhibitors (e.g. ciclosporin and quinidine), digoxin, vasopressin analogues (desmopressin), diuretics
Adverse effects	Aquaretic symptoms (thirst, polyuria, nocturia, polydipsia), drug-induced liver injury, palpitations, constipation, dyspepsia, reduced appetite, gout, hypernatraemia, hyperuricaemia, dry skin, eczema, rash, diarrhoea
Dosage and administration	Oral route. Split-dose regimen. Initiating dose of 60 mg daily (45 mg every morning and 15 mg at night). Uptitrate dose gradually (over weeks to months) to 90 mg daily (60 mg and 30 mg split dose) and then to 120 mg daily (90 mg and 30 mg split dose), based on the patient's tolerance of aquaretic symptoms

ADPKD autosomal dominant polycystic kidney disease CKD chronic kidney disease CYP cytochrome P450

Table 3 **Efficacy of tolvaptan and increased water intake on a decline in the estimated glomerular filtration rate in clinical trials**[4-6]

Parameter	TEMPO 3:4[4]	REPRISE[5]	PREVENT-ADPKD[6]
Therapy investigated	Tolvaptan	Tolvaptan	Increased water intake*
Number of patients	1445	1370	184
Age (years)	18–50	18–65	18–67
Baseline eGFR (mL/min/1.73 m^2)	>60	25–65	>30
Efficacy on decline in renal function (therapy vs placebo or standard)	–2.61 vs –3.81 mg/mL/year	–2.34 vs –3.61 mL/min/1.73 m^2	–2.31 vs –2.38 mL/min/1.73 m^2
Discontinuation (therapy vs placebo or standard treatment)	23% vs 14%	9.5% vs 2.2%	12% vs 16.3%
Adverse effects	Aquaresis (100%) Hepatic injury (4.9%)	Aquaresis (100%) Hepatic injury (5.6%)	Mild reversible hyponatraemia (8.7%)

* Water intake prescribed to reduce 24-hour urine osmolality below 270 mOsmol/kg
eGFR estimated glomerular filtration rate

elements). It fluctuates in intensity, duration and quality, with episodes occurring suddenly and inexplicably. This can be debilitating and cause mental and physical fatigue, reduced quality of life, and depression. The mechanisms of chronic pain are multifactorial:

- kidney capsular distension or intrarenal obstruction due to expanding cysts
- mechanical axial pain caused by an abnormal posture due to large kidneys (with some weighing up to 1–3 kg)
- pain unrelated to the kidneys (inguinal hernia, severe polycystic liver disease, gastro-oesophageal reflux or diverticulitis).

Chronic flank, abdominal or back pain in patients with ADPKD is often overlooked by healthcare providers and it should be screened for at every clinical visit. Management should begin with careful clinical assessment, including the identification of any obvious medical causes and biopsychosocial contributors, such as the presence of anxiety or depression, lack

of social support, and previous experiences of pain.[7] Due to the lack of specific evidence, pharmacological management should follow therapeutic guidelines for managing chronic non-cancer pain (using a multidimensional approach with a sequential trial of analgesics – paracetomol, non-steroidal anti-inflammatory drugs (NSAIDs) and then adjuvants).[7] However, there are some practice points specific for the management of ADPKD:

- the use of NSAIDs should be restricted to a maximum of five continous treatment days per episode of pain in chronic kidney disease Stages 1–3 and on a per-case basis in Stages 4–5 to reduce the risk of precipitating acute-on-chronic kidney failure
- the analgesic dose should be modified according to the glomerular filtration rate
- in some patients, a large dominant kidney cyst (>5 cm in diameter) may be responsible for pain, and cyst aspiration by an interventional radiologist can be highly effective
- pain refractory to analgesics warrants prudent re-assessment and a consideration of referral to a pain specialist.

Conclusion

ADPKD is a common genetic kidney disease and the engagement of patients with their GP is imperative to improve long-term outcomes. In young asymptomatic patients, a focus on lifestyle modifications, the monitoring and treatment of blood pressure, and the selected use of disease-modifying drugs reduce the risk of kidney failure and cardiovascular disease. Chronic pain is a common and overlooked clinical problem in ADPKD. Recognising pain and providing effective pharmacological management can significantly improve the well-being of people with ADPKD. <

Conflicts of interest: Gopi Rangan was a principal investigator of grants from the National Health and Medical Research Council of Australia and conducted a clinical trial on prescribed water intake in ADPKD (GNT1138533, PREVENT-ADPKD study). He was also a principal investigator of a grant to conduct a clinical trial on prescribed water intake in ADPKD funded by Danone Research (France, manufacturer of bottled water). He is Chair, Scientific Advisory Board, PKD Australia (not-for-profit consumer group for patients with PKD). He is also a site investigator for clinical trials conducted with tolvaptan and a recipient of research grant funding from Otsuka Australia (manufacturer of tolvaptan).

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ARTICLE

Drug treatment of cystic fibrosis

SUMMARY

Cystic fibrosis is the most common life-limiting autosomal recessive condition in Australia. A defect in the cystic fibrosis transmembrane conductance regulator protein affects chloride transport across epithelial cells.

Patients with cystic fibrosis produce thick sticky mucus. This causes problems in multiple organs, particularly the lungs.

Cystic fibrosis modulator therapies can partially correct the underlying pathophysiology and improve chloride transport, thereby improving morbidity. Life expectancy is improving, so many patients are now developing chronic diseases associated with ageing.

All health professionals should be aware that the cystic fibrosis modulator therapies are metabolised via cytochrome P450 pathways in the liver. There are therefore significant drug–drug interactions with medicines metabolised by the same pathways.

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cystic fibrosis transmembrane conductance regulator, elexacaftor, ivacaftor, lumacaftor, tezacaftor

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Introduction

Cystic fibrosis is the most common life-limiting autosomal recessive condition in Australia, with a disease incidence of approximately one in 2500 births.[1] Approximately one in 25 people are carriers of a cystic fibrosis gene mutation. While cystic fibrosis was previously fatal in infancy and childhood, its management has significantly improved such that the median life expectancy is now 53 years. In 2020 there were more adults than children living with cystic fibrosis in Australia.[1]

Pathophysiology

Cystic fibrosis is caused by mutations that result in a defect in the cystic fibrosis transmembrane conductance regulator protein. This protein regulates chloride transport across epithelial cells in the lungs, pancreas, intestines, sweat glands and male reproductive tract. Cystic fibrosis is therefore a multiorgan disease. It is classically characterised by chronic airway inflammation and infection, exocrine pancreatic insufficiency with nutrient malabsorption, hepatobiliary dysfunction and male infertility. Death is usually due to respiratory failure, secondary to chronic airway inflammation and infection.[2,3]

Mutations

More than 2000 mutations of the cystic fibrosis transmembrane conductance regulator gene have been identified. However, in Australia at least 90% of patients with cystic fibrosis have the F508del (also known as ΔF508) mutation, with 47% being homozygotes.[2] The next most common mutation (G551D) comprises only 4.2% of individual allele variants.[1]

Major advances in understanding the cystic fibrosis transmembrane conductance regulator have subsequently allowed for classification of mutations into six different categories (Table 1).[2,4,5] For example, the F508del mutation affects the way the regulator protein is folded.

Medical management

Cystic fibrosis is best managed by specialist multidisciplinary teams involving physicians, nurses, dieticians, physiotherapists, pharmacists, social workers and psychologists.[2] The management priorities include maintaining lung health, managing gastrointestinal complications, optimising nutrition by replacing exocrine pancreatic enzymes, and controlling cystic fibrosis-related diabetes.[6]

Treatment has traditionally focused on symptom control and prevention of complications.[2,3] However, drugs to modulate the cystic fibrosis transmembrane conductance regulator are now available to target the underlying dysfunction seen in cystic fibrosis.

Cystic fibrosis modulator therapies

Therapies that modulate the cystic fibrosis transmembrane conductance regulator aim to correct or improve the transport, function and expression of the regulator protein. They may therefore be referred to as correctors or potentiators. Different genotypes are suitable for different modulator therapies, creating a degree of personalised medicine. This can improve outcomes for many patients. However, these new drugs are not curative. Their effects are temporary and, when they are stopped, the dysfunction of the cystic fibrosis transmembrane conductance regulator returns.

Table 1 **Classes of cystic fibrosis mutations**[5]

Class	Effect of mutation	Defect types	Mutation examples	Required approaches
Class I	No functional cystic fibrosis transmembrane conductance regulator protein produced	No protein	G542X R553X W1282X	Rescue protein synthesis
Class II	Cystic fibrosis transmembrane conductance regulator protein misfolded, retained in the endoplasmic reticulum and subsequently degraded	No traffic	G85E Δ1507 ΔF508 N1303K	Correct protein folding
Class III	Impaired cystic fibrosis transmembrane conductance regulator channel regulation/opening	No function	V520F S549R G551D	Restore channel conductance
Class IV	Reduced conduction across channel	Less function	R117H R334W S1235R	Restore channel conductance
Class V	Reduced synthesis of cystic fibrosis transmembrane conductance regulator	Less protein	A455E 1680-886A>G 2657+5G>A	Maturation/correct mis-splicing
Class VI	Decreased cystic fibrosis transmembrane conductance regulator stability	Less stable	rΔF508 Q1412X	Promote protein stability

The new drugs are expensive. The Pharmaceutical Benefits Scheme (PBS) price for a one-month course of modulator therapy is currently around $17,000–21,000.

Ivacaftor

Ivacaftor was the first cystic fibrosis transmembrane conductance regulator modulator approved by the Therapeutic Goods Administration (TGA) in Australia. It is a potentiator which improves chloride transport. Ivacaftor is approved for treatment of a select group of Class III mutations in patients over 12 months old.

Clinical trials showed ivacaftor significantly reduces concentrations of sweat chloride and increases forced expiratory volume in one second (FEV_1) by 10.6%, compared to placebo. It also increases faecal elastase – a marker of exocrine pancreatic function.[7] An open-label extension study found ivacaftor to have persisting benefits in weight gain and lung function with an ongoing reduction in pulmonary exacerbations.[8] Cystic fibrosis registry studies show improved patient survival and reduced transplantation rates with ivacaftor.[9]

Drug interactions

Ivacaftor is a substrate of cytochrome P450 (CYP) 3A4 and CYP3A5 isoenzymes. Drugs that inhibit or induce CYP3A activity will therefore interact with its pharmacokinetics (see Table 2). With strong (e.g. ketoconazole, itraconazole, posaconazole, or clarithromycin) or moderate (e.g. fluconazole or erythromycin) CYP3A inhibitors, ivacaftor will require a less frequent dosing regimen. CYP3A inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital and St John's wort) may reduce the exposure and effectiveness of ivacaftor.

Ivacaftor has weak CYP3A inhibitory effects. Care should therefore be taken with concomitant use of benzodiazepines, as ivacaftor may increase the risk of their adverse effects.

Table 2 **Commonly prescribed drugs with significant CFTR-modulator interactions involving cytochrome P450 3A4**

CYP3A4 inducers	CYP3A4 inhibitors
Barbiturates (phenobarbital)	Azole antifungals
Carbamazepine	Amiodarone
Phenytoin	Erythromycin
Rifampicin	Clarithromycin
St John's wort	Protease inhibitors (ritonavir)

CFTR cystic fibrosis transmembrane conductance regulator
CYP cytochrome P450

Adverse effects

The adverse effects of ivacaftor include headache (24%), abdominal pain (16%), rash (13%), dizziness (9.2%) and more frequent upper respiratory tract infections. Liver dysfunction with a rise in transaminases can also occur.

Ivacaftor/lumacaftor

Ivacaftor/lumacaftor is a combination therapy, comprising both ivacaftor, a potentiator, and lumacaftor, a corrector. Correctors are designed to improve the folding, processing and trafficking of the defective regulator protein in Class II mutations.

Initial trials in F508del homozygous patients reported only a 2.6–4% improvement in FEV_1 and a small increase in weight. However, the combination reduces the rate of pulmonary exacerbations and events leading to hospitalisation or the use of intravenous antibiotics by 30–39%.[10] Extension studies have shown ongoing mild improvement in lung function and body mass index.[11] Ivacaftor/lumacaftor is PBS-listed for F508del homozygous patients over two years old.

Drug interactions

Lumacaftor is a strong inducer of CYP3A. Ivacaftor/lumacaftor may therefore decrease the systemic exposure of products that are substrates of CYP3A. The dose of ivacaftor in the combination takes account of ivacaftor's metabolism by CYP3A. Importantly, ivacaftor/lumacaftor may decrease the effectiveness of oral, injectable, transdermal and implantable hormonal contraceptives. These contraceptives should not be relied on as a sole contraceptive method. Other common drug classes that may be affected by ivacaftor/lumacaftor include antidepressants (citalopram, escitalopram, sertraline), proton pump inhibitors (esomeprazole, omeprazole, lansoprazole) and anticoagulants (warfarin and dabigatran).

Adverse effects

Common adverse effects of the combination include dyspnoea (14%), diarrhoea (11%), nausea (10%) and headache. Potentially serious adverse reactions include hepatobiliary events – transaminase elevations, cholestatic hepatitis and hepatic encephalopathy.

Tezacaftor/ivacaftor, ivacaftor

Tezacaftor/ivacaftor is taken as a fixed-dose combination tablet in the morning with a further dose of ivacaftor in the evening. Tezacaftor, like lumacaftor, improves cellular processing of the cystic fibrosis transmembrane conductance regulator protein so is suitable for Class II mutations.

Phase III placebo-controlled trials in patients homozygous for F508del showed FEV_1 improved by 4% and pulmonary exacerbations reduced by 35%.[12] Tezacaftor/ivacaftor also increased FEV_1 by 6.8% in comparison to ivacaftor monotherapy (4.7%) in patients who were heterozygous for F508del and had a residual function mutation.[13] It has PBS approval for patients over six years old who are homozygous for F508del or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator gene that is 'responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence'.

Drug interactions

Although tezacaftor/ivacaftor is also a CYP3A inducer, it is weak in contrast to ivacaftor/lumacaftor. Consequently, tezacaftor/ivacaftor has relatively fewer significant drug–drug interactions and does not appear to affect hormonal contraceptives.

Adverse effects

The most common adverse effects include headache (13.7%), nasopharyngitis (11.5%) and nausea (7.7%). There was no significant difference in transaminase elevations between tezacaftor/ivacaftor and placebo.

Elexacaftor/tezacaftor/ivacaftor, ivacaftor

Elexacaftor is a corrector. Elexacaftor/tezacaftor/ivacaftor is taken as a fixed-dose combination in the morning with another dose of ivacaftor in the evening. This regimen is suitable for Class II, III, IV and V mutations. It is therefore indicated for all patients with F508del mutations. It has PBS approval for patients over 12 years old.

Three phase III, double-blind, controlled studies reported the regimen had significant clinical benefit, particularly a rapid and sustained improvement in FEV_1 and a reduction in the rate of pulmonary exacerbations when compared to matched controls receiving placebo. One trial was in F508del homozygotes,[14] one was in F508del heterozygotes with a gating or residual function mutation,[15] and one was in F508del heterozygotes with minimal or no-function mutations.[16]

F508del homozygotes had 10% improvement in FEV_1 while taking elexacaftor/tezacaftor/ivacaftor compared with tezacaftor/ivacaftor. Sweat chloride and pulmonary exacerbations also significantly decreased.

Drug interactions

Elexacaftor is a CYP3A substrate and has similar drug interactions to the other modulators. It is not predicted to have clinically significant effects on hormonal contraception.

Adverse effects

Adverse effects of the combination regimen include headache (17.3%), diarrhoea (12.9%), rash (8.9%) and increased liver transaminase concentrations.

Cystic fibrosis and chronic disease

With improvement in life expectancy, patients with cystic fibrosis are increasingly likely to develop chronic health conditions associated with ageing – particularly malignancy and cardiovascular disease. A chronic pro-inflammatory state and intestinal dysbiosis (possibly secondary to prolonged antibiotic therapy) are thought to contribute to a higher incidence of colorectal cancer.[17] Guidelines for screening, including colonoscopy, have consequently been developed.[18]

Patients with cystic fibrosis have higher rates of cardiac sequelae, particularly pulmonary hypertension and right heart dysfunction, which correlates with declining FEV_1.[19] The cystic fibrosis transmembrane conductance regulator has been identified in cardiomyocytes,[20] suggesting there is dysfunction at a cellular level.

Systemic vascular disease is now a more frequent comorbidity of cystic fibrosis,[21] and atherosclerosis and coronary artery disease are likely to continue to increase in prevalence.[22] Microvascular changes are recognised as a complication of diabetes related to cystic fibrosis, especially with renal disease and retinopathy.[23]

How cystic fibrosis modulator therapy affects the development of chronic conditions is not clear. The modulators reduce systemic long-term inflammation, and this may reduce intestinal and cardiovascular dysfunction. However, cystic fibrosis transmembrane conductance regulator modulators also increase body mass index, serum lipids and blood pressure, all of which may predispose to cardiovascular sequelae.[24] Nonetheless, development of cystic fibrosis cardiovascular screening guidelines is clearly warranted.

Future directions

Further advances in cystic fibrosis management are likely to occur in the coming decade. Postmarket experience has shown that cystic fibrosis transmembrane conductance regulator modulators are safe and effective, and their role will likely expand. This will not only be with development of new, more efficacious therapies, but also with extra subgroups of the cystic fibrosis population becoming eligible – for example, at younger ages and for patients with other mutations.

Other small-molecule therapies and gene therapy are potential areas of treatment development in cystic fibrosis.[2] mRNA-based repair of mutations via antisense oligonucleotides may be an effective therapeutic tool, as seen with Duchenne's muscular dystrophy and spinal muscular atrophy. Direct delivery of the cystic fibrosis transmembrane conductance regulator gene to the airway epithelium via inhaled viral vectors also shows promise.[25]

In addition to cystic fibrosis transmembrane conductance regulator-based approaches, ongoing development of novel antimucolytic, anti-inflammatory and antimicrobial therapies will likely contribute to future therapy.

Conclusion

While cystic fibrosis remains a life-limiting disease, the outlook is increasingly positive. Treatment has shifted to improving the structure and function of the cystic fibrosis transmembrane conductance regulator, thereby altering the pathophysiology of the disease.

Cystic fibrosis transmembrane conductance regulator modulators are now a mainstay of management and therapeutic decisions can be based on genotype rather than just phenotype. These new drugs are expensive, and treatment may be limited or delayed by regulatory approval processes and funding negotiations.

With greater life expectancy, patients with concomitant cystic fibrosis and age-associated comorbidities are more likely to present in primary healthcare. It is therefore important for all healthcare professionals to understand cystic fibrosis transmembrane conductance regulator modulators, their potential adverse effects and drug–drug interactions. ≺

Conflicts of interest: none declared

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NEW DRUGS

New drugs

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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.

Amifampridine

Approved indication: Lambert-Eaton myasthenic syndrome

Ruzurgi (Lacuna)
10 mg tablets

Lambert-Eaton myasthenic syndrome can develop in some patients with cancer, particularly small cell lung cancer. There is also an autoimmune form of the syndrome and this sometimes affects children. Both forms are due to an abnormality in the release of presynaptic acetylcholine. This disorder of neuromuscular transmission results in muscle weakness that may present as an abnormal gait and autonomic dysfunction which can present as a dry mouth, constipation or erectile dysfunction.

Amifampridine has been used, through the Special Access Scheme, to manage the symptoms of Lambert-Eaton myasthenic syndrome. It is thought to work by blocking the potassium channels of the presynaptic neuron. This prolongs depolarisation and the influx of calcium ions resulting in the release of acetylcholine.

The dose of amifampridine is based on body weight. It is given in divided doses and titrated to find a balance between symptom relief and adverse effects. Lower doses may be required in patients with variants in the gene for N-acetyltransferase 2. As this enzyme metabolises amifampridine, patients who are 'slow acetylators' will have higher drug concentrations. The elimination half-life of amifampridine is around four hours, with most of the dose being excreted in the urine. The effects of renal and hepatic impairment have not been studied in clinical trials.

Lambert-Eaton myasthenic syndrome is very rare so trials of drug therapy are small. A phase II trial randomised 12 patients to take amifampridine and 14 to take a placebo for six days. Electromyography showed that the amplitude of action potentials increased in patients taking amifampridine. These patients also improved on a quantitative assessment of muscle function.[1]

Another randomised trial studied 32 patients who were already taking amifampridine. A group of 14 continued their usual dose, while 18 patients had their dose tapered to zero over several days and then resumed their usual dose. Tapering off the dose of amifampridine resulted in 72% (13/18) of the patients being at least 30% slower in getting up out of a chair. They also felt much weaker than the 14 patients who continued amifampridine. These effects reversed after the usual dose was resumed.[2]

Some of the adverse effects of amifampridine, such as abdominal pain, may be related to its cholinergic actions. These effects are more likely if the patient is taking other cholinergic drugs, such as cholinesterase inhibitors. As amifampridine can cause seizures, it is contraindicated if there is a history of seizures. The risk of seizures will be increased if the patient is also taking drugs known to lower the seizure threshold. Prolongation of the QT interval is a potential risk. The most frequent adverse events include dysaesthesia, abdominal pain, dyspepsia, dizziness and nausea.

While the evidence for the efficacy of amifampridine is limited, it is also limited for alternative therapies such as pyridostigmine or immunosuppression. Although the effect size is uncertain, amifampridine is recommended as the first-line drug treatment for managing the symptoms of Lambert-Eaton myasthenic syndrome. It has been approved for use in adults and in children at least six years old.

T manufacturer provided relevant information

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

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Anifrolumab

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Approved indication: systemic lupus erythematosus

Saphnelo (AstraZeneca)
vials containing 300 mg concentrated solution for dilution

Type I interferons are cytokines that are implicated in the pathogenesis of systemic lupus erythematosus. Anifrolumab is a fully human immunoglobulin G1 kappa monoclonal antibody that inhibits the signalling of type I interferon receptor subunit 1, thereby inhibiting the activity of all type I interferons. Anifrolumab is indicated as add-on treatment for moderate to severe active systemic lupus erythematosus.

The recommended dose of anifrolumab is 300 mg given as an intravenous infusion over 30 minutes every four weeks. Treatment may be discontinued if there is no improvement in disease control after six months. Anifrolumab is metabolised into small peptides and amino acids by proteolytic enzymes and is unlikely to be metabolised by hepatic enzymes. There have been no studies of anifrolumab in patients with renal or hepatic impairment. No drug–drug interaction studies have been conducted. Concurrent use with biologic therapies has not been studied.

Two randomised, placebo-controlled, phase III trials enrolled patients 18–70 years of age with moderate to severe active systemic lupus erythematosus who were receiving stable treatment consisting of at least one of either prednisone or equivalent, an antimalarial, azathioprine, mizoribine, mycophenolate mofetil or mycophenolic acid, or methotrexate. In the Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP)-1 trial, patients received either anifrolumab 300 mg, anifrolumab 150 mg or placebo every four weeks for 48 weeks. The primary end point was the difference between the proportion of patients who achieved a systemic lupus erythematosus responder index-4 (SRI-4) response at week 52 with anifrolumab 300 mg versus placebo.[1] In the TULIP-2 trial, patients received either anifrolumab 300 mg or placebo every four weeks for 48 weeks. The primary end point of this trial was a response at week 52 defined by the British Isles Lupus Assessment Group (BILAG)–based Composite Lupus Assessment (BICLA).[2]

In the TULIP-1 trial, the primary end point was not reached, as the proportion of patients with an SRI-4 response was similar between the anifrolumab 300 mg (36%, 65/180 patients) and placebo (40%, 74/184 patients) arms. This response was also similar in the anifrolumab 150 mg arm (38%, 35/93 patients), suggesting a lack of efficacy at the lower dose.[1] In the TULIP-2 trial, a BICLA response was noted in 48% of patients in the anifrolumab arm (86/180) and in 32% of patients in the placebo arm (57/182) at week 52. In patients who were taking high-dose prednisone or equivalent at baseline, there was a dose reduction (to 7.5 mg/day or less) from week 40 to week 52 by 52% of patients in the anifrolumab arm (45/87) compared with 30% of patients in the placebo arm (25/83). Among patients with at least moderate cutaneous activity at baseline, a reduction of at least 50% in the Cutaneous Lupus Erythematosus Disease Area and Severity Index was observed in 49% of patients in the anifrolumab arm (24/49) and in 25% of patients in the placebo arm (10/40) at week 12. The annualised rate of flares (defined as worsening in any of nine organ systems in the BILAG index) at week 52 was 0.43 in the anifrolumab arm and 0.64 in the placebo arm.[2]

The most common adverse events in the anifrolumab of the TULIP-2 trial were upper respiratory tract infection (22% vs 10% in the placebo arm), nasopharyngitis (16% vs 11%), infusion-related reactions (14% vs 8%), bronchitis (12% vs 4%) and cutaneous herpes zoster infection (7% vs 1%, resolved without stopping treatment in all cases). These adverse events were serious in 8% of the anifrolumab arm (15/180 patients) and 17% of the placebo arm (31/182 patients). No anaphylactic reactions were reported.[2] Infusions may be stopped or the infusion rate may be reduced to manage infusion reactions. Adverse events led to discontinuation of anifrolumab in 11/180 patients in the TULIP-1 trial and 5/180 patients in the TULIP-2 trial, and one death occurred in each trial due to pneumonia.[1,2]

The safety and efficacy of anifrolumab have not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Malignant neoplasms were reported in 2% of patients in the anifrolumab 300 mg arm of the TULIP-1 trial.[1] As with all therapeutic proteins, immunogenicity may occur. One patient in the anifrolumab arm of the TULIP-2 trial tested positive for antidrug antibodies.[2] It is not recommended to receive live or attenuated vaccines during treatment.

There are limited data in patients 65 years of age and older. There are no data on the effects of anifrolumab on fertility. The safety and efficacy of anifrolumab have not been established in children and pregnant or breastfeeding women.

A monthly dose of anifrolumab in conjunction with usual treatment led to a clinical response in a greater proportion of patients than with placebo in the TULIP-2 trial. The drug is well tolerated with mild to moderate adverse events in most patients that

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can be managed appropriately. The durability of the drug's modest effect and safety beyond 52 weeks are unknown.

T manufacturer provided the product information

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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.

Bilastine

Approved indication: allergic rhinoconjunctivitis, urticaria

Allertine (Menarini)
20 mg tablets

Bilastine is a long-acting antihistamine that has been available in Europe for more than a decade. It is an antagonist of peripheral H_1 receptors, has no effect on muscarinic receptors and probably has limited transit across the blood–brain barrier. Bilastine therefore adds to the choice of less-sedating antihistamines for allergic conditions.[1]

Tablets of bilastine should not be taken with food or fruit juice as its bioavailability may be reduced. There is minimal metabolism with most of the drug being excreted unchanged, mainly in the faeces. No dose adjustment is recommended for patients with hepatic or renal impairment. The mean elimination half-life is 14.5 hours so only one dose a day is needed.

The approval of bilastine includes both seasonal and perennial allergic rhinitis. There have been several trials of bilastine for allergic rhinitis and five of them were included in a systematic review. These were placebo-controlled trials, but four of them also included other antihistamines for comparison. A total of 3329 patients participated.[2]

Bilastine reduced the total symptom score more than a placebo did. It had favourable effects on nasal and non-nasal symptoms. These effects were similar to those of cetirizine, desloratadine and fexofenadine.[2]

The main double-blind trial of bilastine in urticaria involved 525 patients with chronic idiopathic urticaria. They were randomised to take a daily dose of bilastine 20 mg, levocetirizine 5 mg or placebo for 28 days. Both active treatments reduced pruritus and the number and size of wheals.[3]

Most of the efficacy trials were short, but there are now several years of experience with the drug overseas. An open-label extension of a trial in perennial allergic rhinitis followed 513 patients for a year and found bilastine was well tolerated.[4] Common symptoms include headache, dizziness and abdominal pain, but their incidence is similar to that seen with other antihistamines and placebo. Somnolence can occur, but in the systematic review there was no difference from placebo.[2] Bilastine has been reported not to enhance the effects of lorazepam or add to the effects of alcohol on psychomotor performance. Bilastine does not prolong the QT interval on the ECG. While data in pregnancy are limited, animal studies suggest only very high doses affect embryofetal development. Bilastine does enter animal breast milk. The drug is not yet approved for children under 12 years old.

There seems to be no difference in efficacy between bilastine and other antihistamines. It may cause less somnolence than cetirizine, but the incidence is similar to that seen with desloratadine and fexofenadine.[2]

T manufacturer provided the product information

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NEW DRUGS

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Diroximel fumarate

Approved indication: multiple sclerosis

Vumerity (Biogen)
231 mg capsules

Dimethyl fumarate is an oral drug that was approved for the treatment of relapsing multiple sclerosis almost a decade ago. Follow-up data since then show that annual relapse rates remain low with about 70% of patients having no new or enlarging lesions on MRI during seven years of treatment.[1]

The effect of dimethyl fumarate is thought to be due to its active metabolite monomethyl fumarate. This may stimulate antioxidant production and reduce inflammatory responses.

Diroximel fumarate is another molecule that is rapidly hydrolysed to monomethyl fumarate after oral administration. Although food reduces the maximum concentration, capsules of diroximel fumarate can be taken with or without food. Most of the twice-daily dose is expired as carbon dioxide. No dose adjustments are recommended for patients with renal or hepatic impairment. Pharmacokinetic drug interactions are unlikely.

Regulatory authorities have accepted the premise that, as the drugs have the same active metabolite, the efficacy and safety of diroximel fumarate should be similar to that of dimethyl fumarate. Pivotal trials of dimethyl fumarate, such as the DEFINE study,[2] have therefore supported the approval of diroximel fumarate for the treatment of relapsing multiple sclerosis.

Diroximel fumarate is being studied in an open-label, single-arm phase III trial. An interim analysis, involving 696 patients, was carried out after a median of 60 weeks. MRI at 48 weeks showed that the mean number of lesions had reduced. Almost 89% of the patients had not had a relapse.[3]

Approximately 15% of the patients discontinued treatment with 6.3% stopping because of adverse events. The most frequent adverse effects were flushing and gastrointestinal symptoms such as diarrhoea.[3]

As gastrointestinal adverse effects are common with dimethyl fumarate, another study has compared its tolerability with that of diroximel fumarate. This was a double-blind phase III trial. It randomised 253 patients with relapsing-remitting multiple sclerosis to take diroximel fumarate and 251 to take dimethyl fumarate. The patients rated any gastrointestinal symptoms on a scale of 0–10. Over five weeks there were symptoms (with a score of 2 or more) for an average of 1.4 days with diroximel fumarate and 2.6 days with dimethyl fumarate. The proportions of patients affected by gastrointestinal symptoms were 34.8% versus 49%. Four patients (1.6%) stopped treatment with diroximel fumarate because of adverse events compared with 15 (6%) of those taking dimethyl fumarate.[4]

In the open-label trial 7.3% of the patients had lymphopenia for six months.[3] This could increase the risk of infection, so regular blood counts are recommended. Live vaccines are not recommended.

It is possible that some of the rare adverse events seen with dimethyl fumarate will occur with diroximel fumarate. These include progressive multifocal leukoencephalopathy and Fanconi syndrome. Annual urinalysis is recommended to check for proteinuria. The effect of long-term treatment on the disability of multiple sclerosis will need to be studied. It is also unclear what the clinical importance is in regard to the small difference in gastrointestinal symptoms. While diroximel fumarate appears to have greater gastrointestinal tolerability than dimethyl fumarate over five weeks,[4] more patients will have altered liver function (25.9% vs 16.4% for alanine aminotransferase).

T manufacturer provided the product 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, and the European Medicines Agency.

Somatrogon

Approved indication: growth hormone deficiency

Ngenla (Pfizer)
pre-filled pens containing 24 mg/1.2 mL or 60 mg/1.2 mL

In children, growth hormone deficiency may be congenital, acquired or idiopathic. It has several effects including reduced growth resulting in short stature. The children are treated with synthetic human growth hormone (somatropin). This requires daily injections which are painful and distressing for some children. The desire to reduce the frequency of injections has led to the development of long-acting analogues of growth hormone.

Somatrogon contains the amino acid sequence of growth hormone plus three copies of the C-terminal peptide of human chorionic gonadotropin. The C-terminal modification extends the half-life of growth hormone to approximately 28 hours. Somatrogon will remain in circulation for six days, so weekly subcutaneous dosing is possible. The injection should be rotated each week between the abdomen, thighs, upper arms and buttocks. Doses are adjusted according to the concentration of insulin-like growth factor (IGF-1), body weight and growth velocity.

The recommended weekly dose of 0.66 mg/kg is based on an open-label phase II trial involving 53 children with growth hormone deficiency. These children had an average age of about six years. They were randomised to receive daily somatropin or one of three different doses of somatrogon once a week. Over a year, IGF-1 concentrations increased in all groups and the children grew. The efficacy of the recommended dose was similar to that of daily injections of somatropin.[1]

A phase III trial also compared weekly somatrogon with daily somatropin. In this open-label trial 224 previously untreated children, with an average age of 7.72 years, were studied for one year. At the end of the trial, the average annual height velocity was 10.10 cm/year for the 109 children given somatrogon and 9.78 cm/year for the 115 given somatropin. Bone maturation was similar in both groups.[2]

In the phase III trial injection-site reactions were the most frequent adverse events. Injection-site pain was experienced by 39.4% of the somatrogon group and 25.2% of the somatropin group. Erythema and itching at the injection site only occurred in the children given somatrogon. About 77% of this group developed antidrug antibodies, compared with about 16% of the somatropin group, but there was no evidence of neutralising activity. Like other growth hormone products somatrogon may have effects on glucose metabolism and adrenal function. Caution is required if the child requires treatment with a corticosteroid. Somatrogon is contraindicated in acute critical illness and children with cancer.

The phase III trial showed that somatrogon was not statistically inferior to somatropin.[2] While the injections of somatrogon are less frequent they are more painful. Longer term follow-up is needed to address questions about immunogenicity and any effects from not having daily peaks and troughs in growth hormone concentrations. Treatment with somatrogon is recommended to end when there is closure of the epiphyseal growth plates.

T manufacturer provided the product 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 website of the European Medicines Agency.

Aust Prescr 2022;45:181
https://doi.org/10.18773/austprescr.2022.061
First published 1 September 2022

NEW DRUGS

Aust Prescr 2022;45:182
https://doi.org/10.18773/austprescr.2022.058
First published 1 September 2022

Tixagevimab and cilgavimab

Approved indication: COVID-19 prophylaxis
Evusheld (AstraZeneca)
vials containing tixagevimab 100 mg/mL solution
vials containing cilgavimab 100 mg/mL solution

Immunisation remains the best protection against severe COVID-19, however some people may not have an adequate immune response to the current vaccines. They include those who are immunocompromised or taking immunosuppressant drugs. There is also a need for alternative prophylaxis for people who have had a severe adverse reaction to a COVID-19 vaccine. One approach is to give antibodies to people at risk. The combination of casirivimab and imdevimab has already been used in post-exposure prophylaxis while the combination of tixagevimab and cilgavimab has been approved for pre-exposure prophylaxis.

Tixagevimab and cilgavimab are monoclonal antibodies that bind to different regions of the spike protein of SARS-CoV-2. After intramuscular injection of the two drugs at separate sites, it takes approximately two weeks for the two antibodies to reach their maximum concentrations. However, a protective concentration may be reached six hours after gluteal injection. Both drugs are cleared like other antibodies. The elimination half-life of tixagevimab is 89 days and it is 84 days for cilgavimab. Following injection of the two antibodies, the duration of protection against infection is thought to be at least six months.

The efficacy and safety of tixagevimab and cilgavimab are being assessed in a phase III trial.[1] A preliminary efficacy analysis, a median of 83 days after injection, included 3441 adults given 150 mg tixagevimab and 150 mg cilgavimab, and 1731 given placebo. These participants had an average age of 53.5 years with most having conditions that placed them at a high risk of severe COVID-19. In the preliminary analysis, symptomatic infection with SARS-CoV-2 occurred in eight (0.2%) of the people given antibodies and 17 (1%) of those given placebo. None of the infections was severe in the antibody group. Analysis at a median follow-up of six months showed a relative risk reduction of 82.8% for developing symptomatic COVID-19 following injections of tixagevimab and cilgavimab.[1]

Adverse event rates were similar for the antibodies and placebo. Injection-site reactions occurred in 2.4% of the antibody group and 2.1% of the placebo group.[1] Although the incidence was low, a greater proportion of those given the antibodies had serious cardiovascular adverse events such as heart failure.

The last participant in the phase III trial was injected in March 2021.[1] Since then the pattern of the pandemic has changed with Omicron now being the most frequent variant of the virus. While tixagevimab and cilgavimab will have some activity against the Omicron variant, it may be reduced. The US Food and Drug Administration has therefore recommended using a higher dose than that studied in the trial.[2]

Although the combination is approved for immunocompromised patients, less than 4% of the trial participants were taking immunosuppressive therapy or had immunosuppressive disease.[1] It is not approved for children under 12 years old. There is also little information about using the combination during pregnancy or lactation. The Australian approval of the combination is provisional as there is a need for evidence of long-term efficacy and safety including any development of viral resistance.

T manufacturer provided the AusPAR and the product 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.

Corrections

Approach to the diagnosis of secondary hypertension in adults [Correction]

Aust Prescr 2022;45:183
https://doi.org/10.18773/austprescr.2022.055
First published 18 August 2022

The article on secondary hypertension (Aust Prescr 2021;44:165-9) has been corrected.
View corrected article.

There was an error in Table 2 – Factors that may lead to false-positive or false-negative aldosterone:renin ratio results. In the 'Potassium wasting diuretics' line, the arrow in the 'Effect on aldosterone:renin ratio' column should point down (not up), indicating a false negative.

Trifarotene for acne [Correction]

Aust Prescr 2022;45;183
https://doi.org/10.18773/austprescr.2022.064

The new drug comment for trifarotene (Aust Prescr 2021;44:140-1) has been corrected.
View corrected article.

The brand name was misspelt. It should have been Aklief (not Alkief).

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