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Introduction

At least 8000 people in Australia currently have acute rheumatic fever or rheumatic heart disease. The conditions are notifiable in the Northern Territory, Western Australia, Queensland, South Australia and New South Wales. The Rheumatic Heart Disease Control Programs in these jurisdictions are important sources of support for healthcare providers. Nationally, Rheumatic Heart Disease Australia provides educational resources for providers, patients and families. Important changes were made to the therapeutic recommendations in the 2020 Australian Guideline for Prevention, Diagnosis and Management of Acute Rheumatic Fever and Rheumatic Heart Disease. The duration of secondary prophylaxis after a diagnosis of acute rheumatic fever or rheumatic heart disease is now shorter for some people without cardiac involvement. Non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen or ibuprofen are now the recommended first-line drugs for arthritis instead of aspirin. Lidocaine (lignocaine) is no longer contraindicated with intramuscular injections of benzathine benzylpenicillin G. Endocarditis prophylaxis is now recommended for all patients with rheumatic heart disease, not just for Aboriginal and Torres Strait Islander people.

What is rheumatic fever and who gets it?

In less than 10% of the population, infection with Streptococcus pyogenes (group A streptococcus) can trigger autoimmune conditions including acute rheumatic fever or acute post-streptococcal glomerulonephritis days to months after the initial infection. Acute rheumatic fever is not a homogenous condition and shows high immunological and clinical diversity. It can also be subtle and mimic other conditions. There is no dedicated diagnostic test, and instead it is diagnosed using the Jones criteria. These factors make the diagnosis highly challenging. In up to 75% of people with rheumatic heart disease, previous acute rheumatic fever was unrecognised. The abnormal immune responses characterising acute rheumatic fever chiefly occur in immature immune systems, with the peak incidence occurring at 5–14 years of age. The risk increases with repeated exposure to streptococci. Most cases occur when the exposure risk is high, such as in crowded living conditions or when there is inadequate access to sanitation facilities and health care. Acute rheumatic fever also affects adults. Approximately 7% of notifications in Australia are in 35–44 year olds. In Australia, nearly 90% of acute rheumatic fever cases and 70% of rheumatic heart disease diagnoses.
are in Aboriginal and Torres Strait Islander people. Migrants or second-generation Australians from regions with a high streptococcal burden and low-income countries, especially Maori and Pacific Islander populations, also have an elevated risk (Box).2

**Diagnosis**

The diagnosis of acute rheumatic fever requires actively excluding alternative diagnoses, followed by applying the Jones criteria,6 which can be facilitated using the ARF RHD Guideline mobile phone app. The role of echocardiography in diagnosis and follow-up has become increasingly emphasised.

In Australia, approximately 50% of cases involve a fever with joint pain.11 Joint pain associated with rheumatic fever may be subtle (no heat, effusion or erythema of the joints; only pain and limping) or florid with classical migratory polyarthritis, predominantly affecting large joints. Carditis with arthritis is the next most common manifestation, followed in decreasing order by chorea, carditis alone or other combinations of these ‘major’ Jones criteria. Erythema marginatum and subcutaneous nodules are reported in less than 1% of local cases.12 Carditis alone may comprise only fever with evidence of valve disease, such as mitral valve thickening and mild regurgitation on echocardiography. It may manifest with or without a murmur and with or without a conduction abnormality seen on electrocardiography, such as first-degree heart block. Acute rheumatic fever should therefore be considered in a child with a high risk of streptococcal exposure presenting with unexplained fever. Electrocardiography, measurements of inflammatory markers (C-reactive protein concentrations, erythrocyte sedimentation rate), streptococcal serologic tests and echocardiography may all be indicated for investigation, as fever can be the only sign that the child has acute rheumatic fever.

Sydenham chorea is a neuropsychiatric manifestation of acute rheumatic fever characterised by chorea, decreased muscle tone and sometimes psychiatric and behavioural symptoms. It may occur weeks to months after the onset of streptococcal infection depending on the history of disease recurrence and time of diagnosis, and thus fever, elevated concentrations of inflammatory markers and elevated streptococcal serology may be absent.

**Management of acute rheumatic fever**

Symptom management is critical to reduce morbidity and return children home and to school. The goals of acute rheumatic fever therapy are to:

- relieve symptoms
- mitigate cardiac damage
- eradicate the inciting streptococcal infection
- prevent future recurrences.

Hospitalisation for rheumatic fever is recommended to confirm the diagnosis and facilitate prompt access to an echocardiogram. A variety of doctors (paediatricians, physicians, cardiologists, GPs) with

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**Box**  Groups at risk of acute rheumatic fever and rheumatic heart disease

**At high risk**

- People living in an acute rheumatic fever-endemic setting*
- Aboriginal and Torres Strait Islander people living in rural or remote areas
- Aboriginal and Torres Strait Islander people and Maori and Pacific Islander people living in metropolitan households affected by crowding or low socioeconomic status
- Patients with a personal history of acute rheumatic fever or rheumatic heart disease and <40 years of age

**May be at high risk**

- Family or household recent history of acute rheumatic fever or rheumatic heart disease
- People with household overcrowding (>2 people/bedroom) or low socioeconomic status
- Migrants or refugees from low- or middle-income countries and their children

**Additional factors that increase risk**

- Previous residence in a high-risk setting
- Frequent or recent travel to a high-risk setting
- Age 5–20 years (peak years for developing acute rheumatic fever)

* This refers to communities where the rates of acute rheumatic fever and rheumatic heart disease are high (for example, an acute rheumatic fever incidence higher than 30/100,000 per year in those aged 5–14 years and a rheumatic heart disease all-age prevalence higher than 2/1000).

Source: reproduced from reference 2 with permission
experience in endemic settings may have specialty knowledge of rheumatic fever, which should be sought to guide diagnosis and management.

**Arthritis**

Naproxen and ibuprofen are the recommended first-line anti-inflammatory analgesics for rheumatic arthritis (Table 1). Aspirin is now used second line due to its less favourable safety profile. Initial high-dose NSAID therapy, weaned after 1–2 weeks, is usual. Proton pump inhibitor therapy for gastric protection can be considered for patients requiring prolonged anti-inflammatory treatment.

The duration of treatment is guided by the disease severity, clinical response and concentrations of inflammatory markers (C-reactive protein, erythrocyte sedimentation rate). Most episodes of acute rheumatic fever resolve within six weeks and 90% resolve within 12 weeks. A rebound in inflammatory symptoms can occur on ceasing treatment, requiring the drugs to be re-introduced.²,¹³

**Carditis**

There is no targeted drug therapy available for cardiac valve damage during the acute inflammatory stage. Hydroxychloroquine has been used as a targeted disease-modifying agent¹⁴ based on promising in vitro findings,¹⁵ but clinical trial data are not yet available. For severe carditis, corticosteroids are recommended (Table 1). However, meta-analyses have suggested their lack of benefit in preventing subsequent rheumatic heart disease,²⁶,²⁷ although the studies were mostly performed before the availability of echocardiography. Expert opinion recommends corticosteroids for carditis associated with heart failure.² If NSAIDs have been prescribed for pericarditis or arthritis, these can be discontinued when corticosteroids are started, as corticosteroids provide effective relief of the manifestations of acute rheumatic fever. Proton pump inhibitor therapy can be considered for gastric protection in patients requiring prolonged corticosteroid treatment. Screening for and the management of latent infections (e.g. hepatitis B, strongyloidiasis, tuberculosis) are required before or on starting immunosuppressive corticosteroid doses.²

**Chorea**

Pharmacotherapy is not needed for mild chorea. For more severe cases, carbamazepine is recommended as first-line treatment due to its safety profile, followed by sodium valproate (Table 1). A treatment response may not be observed for 1–2 weeks, and drugs may only reduce, not eliminate, chorea. Treatment should be continued for 2–4 weeks after chorea has subsided, and then be withdrawn. Corticosteroids have reported benefits for severe or refractory chorea and are therefore recommended if the response to carbamazepine or sodium valproate is insufficient (Table 1).¹⁸ Intravenous immunoglobulin and plasmapheresis might be beneficial experimental immunotherapies for Sydenham chorea.²

**Antibiotics**

As rheumatic fever is associated with group A streptococci, antibiotics play a key therapeutic role. S. pyogenes remains susceptible to penicillin, as it is unable to genetically express resistance to penicillin.¹⁹

**Treatment and prevention of streptococcal infection**

The inciting streptococcal infection can be treated with the first dose of benzathine benzylpenicillin G administered for ongoing secondary prophylaxis. Other options are presented in Table 1.

Secondary antibiotic prophylaxis is the mainstay of treatment for acute rheumatic fever and rheumatic heart disease globally to prevent recurrences of rheumatic fever and thereby prevent cumulative valve damage with the development or progression of rheumatic heart disease.²⁰ The recommended regimen is intramuscular injections of benzathine benzylpenicillin G every four weeks for a minimum of five years (if there is no cardiac involvement) or 10 years (if there is cardiac involvement) after the last acute rheumatic fever episode or until 21 years of age, whichever is longer (Table 2).²¹ The recurrence rates of acute rheumatic fever are significantly reduced by this regimen compared to a placebo²² or oral penicillin.²³ Increasing adherence to benzathine benzylpenicillin G is associated with improved rheumatic fever outcomes.²⁴ Regular oral penicillin is not as effective as benzathine benzylpenicillin G.²⁵ This is potentially due to the serum penicillin concentrations achieved and problems with adherence.

**Non-beta-lactam antibiotic options**

An estimated 3.2% of people have an allergic reaction to penicillin and 0.2% have anaphylactic reactions.²,²⁶ These people require alternative antibiotics. Macrolide antibiotics (erythromycin, roxithromycin, azithromycin and clarithromycin) are favoured alternatives in people with adverse reactions to beta-lactams due to their tolerability and dosing regimen. They cover approximately 88% of S. pyogenes isolates (Northern Territory Top End antibiogram data) due to the development of class resistance to macrolides and clindamycin in some isolates. The proportion of S. pyogenes resistant to macrolides in any region is related to local prescribing practices.⁴ As long as most S. pyogenes isolates remain susceptible, macrolides are an acceptable second-line option.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug options listed in order of preference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eradication of inciting streptococcal infection</td>
<td>1. Benzathine benzylpenicillin G 1,200,000 units (child &lt;20 kg: 600,000 units, ≥20 kg: 1,200,000 units) intramuscularly, single dose OR 2. Phenoxymethylpenicillin 500 mg (child: 15 mg/kg up to 500 mg) orally, every 12 hours for 10 days OR 3. For patients with penicillin hypersensitivity (non-severe): cefalexin 1 g (child: 25 mg/kg up to 1 g) orally, every 12 hours for 10 days OR 4. For patients with immediate penicillin hypersensitivity: azithromycin 500 mg (child: 12 mg/kg up to 500 mg) orally, daily for 5 days</td>
<td>Streptococcal infection may not be evident by the time acute rheumatic fever manifests (e.g. cultures often negative), but eradication therapy for possible persisting streptococci is recommended. Intramuscular penicillin is preferred as streptococcal eradication therapy due to better adherence and its subsequent ongoing use in secondary prophylaxis. Between 3% and 30% of group A streptococcus isolates internationally are resistant to macrolide antibiotics (e.g. azithromycin).</td>
</tr>
<tr>
<td>Initial analgesia while awaiting diagnostic confirmation:</td>
<td>Paracetamol 1000 mg (in children: 15 mg/kg) orally, every four hours as needed up to a maximum of 60 mg/kg/day or 4000 mg/day OR Tramadol immediate-release 50–100 mg (in children: 1–2 mg/kg) orally, every four hours as needed up to a maximum of 400 mg/day</td>
<td>Initial analgesia is preferred during diagnostic uncertainty to avoid the masking effect that anti-inflammatory use can have on migratory joint symptoms, fever and concentrations of inflammatory markers. Tramadol (or codeine) is usually avoided in children &lt;12 years of age due to variable metabolism. Use only when strong analgesia is essential and cautious monitoring is available.</td>
</tr>
<tr>
<td>Symptomatic management of arthritis/arthralgia after confirmation of acute rheumatic fever diagnosis</td>
<td>1. Naproxen immediate-release 250–500 mg (in children: 10–20 mg/kg/day) orally twice daily, up to a maximum of 1250 mg daily OR 2. Ibuprofen 200–400 mg (in children: 5–10 mg/kg) orally three times daily, up to a maximum of 2400 mg daily OR 3. Aspirin 50–60 mg/kg/day orally, in 4–5 divided doses in adults and children. Dose can be escalated up to a maximum of 80–100 mg/kg/day in 4–5 divided doses</td>
<td>Naproxen may be safer than aspirin and convenient due to twice-daily dosing and the availability of oral suspension. Ibuprofen is well tolerated and readily available, but there are less data and experience with its use for acute rheumatic fever than those associated with naproxen. The dose of NSAIDs needed for acute rheumatic fever is generally higher than the dose recommended for other conditions; therefore, it may be appropriate to start at the higher dose range. Due to the rare possibility of Reye’s syndrome in children, aspirin may need to be discontinued during intercurrent acute viral illness; thus, influenza vaccination is strongly recommended to reduce the likelihood of this case.</td>
</tr>
<tr>
<td>Symptomatic management of moderate to severe chorea</td>
<td>1. Carbamazepine 3.5–10 mg/kg per dose orally twice daily OR 2. Sodium valproate 7.5–10 mg/kg per dose orally twice daily</td>
<td>Treatment of Sydenham chorea should be considered if movements interfere substantially with normal activities.</td>
</tr>
<tr>
<td>Symptomatic management of very severe chorea or chorea paralytica</td>
<td>In addition to an anticonvulsant drug, consider adding a corticosteroid: Prednisolone 1–2 mg/kg up to a maximum of 80 mg orally once daily</td>
<td></td>
</tr>
</tbody>
</table>

Continued over page
### Table 1  Drugs used for rheumatic fever (continued)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug options listed in order of preference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic management of carditis</td>
<td>Paediatric dosing:</td>
<td>Treatment of heart failure may be required for severe, acute carditis. Seek advice from a specialist cardiologist.</td>
</tr>
<tr>
<td></td>
<td>• Furosemide (frusemide) 1–2 mg/kg orally as a single dose, then 0.5–1 mg/kg (to a maximum of 6 mg/kg) orally every 6–24 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Spironolactone 1–3 mg/kg (initially) up to 100 mg orally in 1–3 divided doses daily. Round dose to a multiple of 6.25 mg (a quarter of a 25-mg tablet)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Enalapril 0.1 mg/kg orally in 1 or 2 divided doses daily, increased gradually over 2 weeks to a maximum of 1 mg/kg orally in 1 or 2 divided doses daily. Alternative ACE inhibitors: captopril, lisinopril</td>
<td>The choice of ACE inhibitor will vary depending on the clinical situation. Seek advice from a specialist cardiologist.</td>
</tr>
<tr>
<td></td>
<td>Adult dosing:</td>
<td>The management of acute carditis follows the same principles as those for the management of acute heart failure. This table provides a guide to the initial management of acute heart failure due to acute carditis in adults. Seeking advice from a specialist cardiologist early is strongly recommended.</td>
</tr>
<tr>
<td></td>
<td>• Furosemide (frusemide) 20–40 mg orally or intravenously as a single dose followed by 20–40 mg orally or intravenously every 8–12 hours. Ongoing dose adjustment is based on clinical progression and renal function.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Spironolactone may be added for patients with limited or no response to loop diuretic; 12.5–200 mg orally once daily with dose escalation based on clinical and electrolyte responses.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Nitrate therapy may be added for patients with limited or no response to diuretic therapy and systolic blood pressure greater than 90 mmHg. Intravenous or topical glyceryl trinitrate may be used.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ACE inhibitor therapy with perindopril or ramipril is recommended in patients with moderate or severe left ventricular systolic dysfunction, unless contraindicated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Digoxin 15 micrograms/kg orally as a single dose, then 5 micrograms/kg after 6 hours, then 3–5 micrograms/kg (in adults: 125–250 micrograms) orally, daily</td>
<td>Digoxin is rarely used for the treatment of acute carditis. Seek advice from a specialist cardiologist.</td>
</tr>
<tr>
<td>Disease-modifying (immunomodulatory) treatments</td>
<td>Prednisolone 1–2 mg/kg up to a maximum of 80 mg orally, once daily</td>
<td>Considered for use in selected cases of severe carditis, despite meta-analyses in which the overall benefit was not evident.</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>1. Benzathine benzylpenicillin G by deep intramuscular injection 1,200,000 units (≥20 kg) or 600,000 units (&lt;20 kg)† OR 2. Phenoxymethylpenicillin (penicillin V) 250 mg orally twice daily OR 3. For patients with penicillin hypersensitivity (non-severe) or immediate penicillin hypersensitivity; erythromycin 250 mg orally twice daily</td>
<td>Every 28 days. Every 21 days for selected groups. Intramuscular penicillin is preferred due to greater effectiveness in head-to-head trial and better adherence.</td>
</tr>
</tbody>
</table>

NSAID non-steroidal anti-inflammatory drug

* For children weighing less than 10 kg, a dose of 600,000 units is still generally recommended, but seek paediatric advice for careful planning of the secondary prophylaxis regimen.

† Patients on 28-day regimens can be recalled from 21 days to help ensure that injections are given by day 28.

‡ Benzathine benzylpenicillin G given every 21 days may be considered for:
  • patients who have breakthrough acute rheumatic fever despite complete adherence to a 28-day regimen
  • patients who are at a high risk of adverse consequences if acute rheumatic fever occurs (have severe rheumatic heart disease or a history of heart valve surgery).

Source: modified from reference 2 with permission
Table 2  Recommended duration of secondary prophylaxis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Definition</th>
<th>Duration of prophylaxis</th>
<th>Conditions for ceasing prophylaxis ‡</th>
<th>Timing of echocardiography after cessation †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible acute rheumatic fever (without cardiac involvement)</td>
<td>Incomplete features of acute rheumatic fever with a normal echocardiogram and normal ECG† throughout acute rheumatic fever episodes</td>
<td>12 months (then reassess)</td>
<td>No signs and symptoms of acute rheumatic fever within the previous 12 months Normal echocardiogram</td>
<td>At 1 year</td>
</tr>
<tr>
<td>Probable acute rheumatic fever (without cardiac involvement)</td>
<td>Highly suspected acute rheumatic fever with a normal echocardiogram</td>
<td>Minimum of 5 years after the most recent episode of probable acute rheumatic fever, or until 21 years of age (whichever is longer)</td>
<td>No probable or definite acute rheumatic fever within the previous 5 years Normal echocardiogram</td>
<td>At 1, 3 and 5 years</td>
</tr>
<tr>
<td>Definite acute rheumatic fever (without cardiac involvement)</td>
<td>Acute rheumatic fever with a normal echocardiogram and normal ECG† throughout acute rheumatic fever episodes</td>
<td>Minimum of 5 years after the most recent episode of acute rheumatic fever, or until 21 years of age (whichever is longer)</td>
<td>No probable or definite acute rheumatic fever within the previous 5 years Normal echocardiogram</td>
<td>At 1, 3 and 5 years</td>
</tr>
<tr>
<td>Definite acute rheumatic fever (with cardiac involvement)</td>
<td>Acute rheumatic fever with carditis or rheumatic heart disease on echocardiography, or with atrioventricular conduction abnormality on ECG† during acute rheumatic fever episodes</td>
<td>According to the severity of rheumatic heart disease (borderline, mild, moderate, severe)</td>
<td>No probable or definite acute rheumatic fever within the previous 10 years Normalisation of echocardiogram after a minimum of 2 years of follow-up</td>
<td>Medical review and repeat echocardiogram at 1–2 years after diagnosis, and 1–2 years after stopping secondary prophylaxis</td>
</tr>
<tr>
<td>Borderline rheumatic heart disease (in people ≤20 years of age only)</td>
<td>Borderline rheumatic heart disease on echocardiography without a documented history of acute rheumatic fever</td>
<td>In a high-risk setting: minimum of 2 years following the diagnosis of borderline rheumatic heart disease If borderline rheumatic heart disease is still present at 2 years, continue for another 2 years and reassess. Seek specialist input §</td>
<td>No probable or definite acute rheumatic fever within the previous 10 years Normalisation of echocardiogram after a minimum of 2 years of follow-up</td>
<td>At 1, 3 and 5 years</td>
</tr>
<tr>
<td>Mild rheumatic heart disease §</td>
<td>Mild rheumatic heart disease on echocardiography or atrioventricular conduction abnormality on ECG† during acute rheumatic fever episodes</td>
<td>If there is a documented history of acute rheumatic fever: minimum of 10 years after the most recent episode of acute rheumatic fever, or until 21 years of age (whichever is longer) If there is NO documented history of acute rheumatic fever and age is &lt;35 years: minimum of 5 years following the diagnosis of rheumatic heart disease or until 21 years of age (whichever is longer)</td>
<td>No probable or definite acute rheumatic fever within the previous 10 years and no progression of rheumatic heart disease Stable echocardiographic features for 2 years</td>
<td>At 1, 3 and 5 years</td>
</tr>
</tbody>
</table>

Continued over page
### Table 2  Recommended duration of secondary prophylaxis (continued)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Definition</th>
<th>Duration of prophylaxis</th>
<th>Conditions for ceasing prophylaxis †</th>
<th>Timing of echocardiography after cessation ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate rheumatic heart disease# **</td>
<td>Moderate rheumatic heart disease on echocardiography</td>
<td>If there is a documented history of acute rheumatic fever: minimum of 10 years after the most recent episode of acute rheumatic fever or until 35 years of age (whichever is longer) If there is no documented history of acute rheumatic fever and age is &lt;35 years: minimum of 5 years following the diagnosis of rheumatic heart disease or until 35 years of age (whichever is longer)</td>
<td>No probable or definite acute rheumatic fever within the previous 10 years Stable echocardiographic features for 2 years</td>
<td>Initially every 12 months</td>
</tr>
<tr>
<td>Severe rheumatic heart disease** † †</td>
<td>Severe rheumatic heart disease on echocardiography OR Previous valve repair or prosthetic valve replacement</td>
<td>If there is a documented history of acute rheumatic fever: minimum of 10 years after the most recent episode of acute rheumatic fever or until 40 years of age (whichever is longer) If there is no documented history of acute rheumatic fever: minimum of 5 years following the diagnosis of rheumatic heart disease or until 40 years of age (whichever is longer)</td>
<td>Stable valvular disease/ cardiac function on serial echocardiography for 3 years OR Patient or family preference to cease due to advancing age or end-of-life care</td>
<td>Initially every 6 months</td>
</tr>
</tbody>
</table>

* All people receiving secondary prophylaxis require a comprehensive clinical assessment and echocardiogram before cessation. Risk factors including future exposure to environments with a high burden of group A streptococcus must be considered.
† Echocardiography may be more frequently performed based on the clinical status and specialist review.
‡ 'Normal ECG' indicates that there is no atrioventricular conduction abnormality during the acute rheumatic fever episode, including first-degree heart block, second-degree heart block, third-degree (complete) heart block or an accelerated junctional rhythm.
§ An update in March 2022 recommends secondary prophylaxis for people ≤20 years of age living in high-risk settings without a documented history of acute rheumatic fever but who have an echocardiogram showing borderline rheumatic heart disease.#
# Prophylaxis may be considered for longer in women considering pregnancy who live in high-risk circumstances for acute rheumatic fever.
¶ If diagnosed with mild or moderate rheumatic heart disease and aged ≥35 years (without acute rheumatic fever), secondary prophylaxis is not required.
** Rarely, moderate or severe rheumatic heart disease may improve on echocardiography without valve surgery. In these cases, the conditions for ceasing prophylaxis can change to follow the most recent severity category. For instance, if moderate rheumatic heart disease improves to mild on echocardiography, recommendations for mild rheumatic heart disease can then be followed.
†† The risk of acute rheumatic fever recurrence is low in people ≥40 years of age; however, lifelong secondary prophylaxis is usually recommended for patients who have had, or are likely to need, heart valve surgery.
†‡ If a person is diagnosed with severe rheumatic heart disease at ≥40 years of age (without acute rheumatic fever), specialist input is required to determine the need for secondary prophylaxis.

Source: reproduced from reference 2 with permission
For non-severe penicillin hypersensitivity, use cefalexin to treat the inciting streptococcal infection and erythromycin for secondary prophylaxis. For immediate penicillin hypersensitivity, use azithromycin to treat the inciting streptococcal infection and erythromycin for secondary prophylaxis (Table 1).

**Management of rheumatic heart disease**

Secondary antibiotic prophylaxis is the only treatment confirmed to be associated with a long-term reduction in the severity of rheumatic heart disease. Patients with moderate to severe rheumatic heart disease require cardiology services and regular echocardiographic follow-up. Women with rheumatic heart disease who are pregnant or of childbearing age require pre-conception counselling and specialist care. Comprehensive guidance on medical and surgical management is detailed in the 2020 Australian Guideline for Acute Rheumatic Fever and Rheumatic Heart Disease.

**Prevention of infective endocarditis**

Rheumatic heart disease poses a risk for infective endocarditis. Certain dental and other invasive surgical procedures can cause transient bacteremia, leading to infection of damaged or prosthetic valves. Guidelines have oscillated on antibiotic prophylaxis for infective endocarditis. The weight of evidence now favours antibiotic use for infective endocarditis prophylaxis in all patients with rheumatic heart disease undergoing high-risk dental or other surgical procedures. Amoxicillin is the recommended first-line drug for endocarditis prophylaxis for certain dental procedures in patients with specified cardiac conditions including rheumatic heart disease, even in those receiving benzathine benzylpenicillin G for secondary prophylaxis (Table 3). However, if a patient has recently had a course of treatment with penicillin, amoxicillin or another beta-lactam (providing higher antibiotic concentrations than prophylactic doses), clindamycin is the recommended first-line drug. This is because the treatment course may have reduced the amoxicillin susceptibility of viridans streptococci, which are commensal oral organisms that can be mobilised into the bloodstream following dental procedures.

**Conclusion**

Practitioners in Australia might encounter cases of acute rheumatic fever and rheumatic heart disease. Those practising in high-burden settings, especially remote Aboriginal and Torres Strait Islander communities, need a low threshold for suspecting these conditions and familiarity with guidelines and resources. Rheumatic Heart Disease Control Programs and Rheumatic Heart Disease Australia can assist practitioners, address clinical queries and provide resources.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug</th>
<th>Time before the procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>For endocarditis prophylaxis</td>
<td>Amoxicillin 2 g (in children: 50 mg/kg up to 2 g)</td>
<td>60 minutes</td>
</tr>
<tr>
<td>For patients with delayed non-severe hypersensitivity to penicillins, cefalexin can be used in most cases</td>
<td>Cefalexin 2 g (in children: 50 mg/kg up to 2 g)</td>
<td>60 minutes</td>
</tr>
<tr>
<td>For patients with immediate (severe or non-severe) or delayed severe hypersensitivity to penicillins</td>
<td>Clindamycin 600 mg (in children: 20 mg/kg up to 600 mg)</td>
<td>60–120 minutes</td>
</tr>
<tr>
<td>For patients who have recently received a treatment-dose course of a beta-lactam antibiotic</td>
<td>Clindamycin 600 mg (in children: 20 mg/kg up to 600 mg)</td>
<td>60–120 minutes</td>
</tr>
</tbody>
</table>

* See Therapeutic Guidelines: Antibiotic, Box 2.13 ‘Procedures for which endocarditis prophylaxis is recommended for patients with a cardiac condition’ for a list of the dental procedures for which endocarditis prophylaxis is recommended in patients with rheumatic heart disease. For endocarditis prophylaxis for other procedures, see eTG.

† See Therapeutic Guidelines: ‘Endocarditis prophylaxis regimens for dental procedures’ for details on intramuscular or intravenous options.

‡ There is some evidence to suggest that moxifloxacin may be used as an alternative to clindamycin in patients with immediate (severe) or non-severe or delayed hypersensitivity to penicillins, but this has not been validated.

Source: modified with permission from reference 2, which includes intravenous and intramuscular options.
ARTICLE

Therapeutics for rheumatic fever and rheumatic heart disease

REFERENCES


Full text free online at nps.org.au/australian-prescriber
Letters to the Editor

Multimodal interventions for pain management

Aust Prescr 2022;45:113
https://doi.org/10.18773/austprescr.2022.045

Regarding the management of pain in older people, GPs are often advised to avoid opioids. This is not realistic for many patients, especially those who have taken opioids long term.

It should always be considered, in any age group, whether there is an appropriate procedure that may help, such as injections, radio frequency and joint surgeries. In addition, many patients who complain of pain are also depressed (as opposed to the many who have depression but do not complain) so treating depression (including options such as transcranial magnetic stimulation and ECT) always needs to be considered. A generalised chronic pain syndrome can occur in the elderly and mental health is key. Pain management programs should also not exclude the elderly. It is important to avoid therapeutic nihilism in the elderly and at least think of all the options that may be offered to younger people.

Sarah Abrahamson
Rehabilitation physician, Victorian Rehabilitation Centre, Glen Waverley, Vic.

REFERENCE


Gloria Wong, the author of the article, comments:

The article focused on the pharmacological management of chronic non-cancer pain in the elderly. While non-pharmacological and interventional approaches were outside the scope of the article, they are nevertheless important in the holistic care of the elderly. The article contained some references for readers interested in these interventions.

The article highlighted the importance of a balanced, evidence-based approach, with careful consideration of the risks associated with pharmacotherapy in older people with chronic pain. ‘Choosing wisely’ is by no means nihilistic.
Off-label drugs for obesity

Aust Prescr 2022;45:114
https://doi.org/10.18773/austprescr.2022.046

We do not believe the article ‘Medicines for long-term obesity management’ is consistent with the NPS MedicineWise philosophy, to provide independent and evidence-based advice to health professionals.

The concluding statement ‘They [weight-loss drugs] are useful during the weight loss phase, but are essential in the maintenance phase’ is contentious but presented as fact. Despite these drugs being used for decades, there are still no trials reporting their benefit on end points, such as cardiovascular events and death. A Cochrane review of their long-term effects in people with hypertension found only one randomised trial reporting cardiovascular outcomes. This showed no differences in all-cause mortality or cardiovascular mortality or morbidity. Some drugs, such as topiramate, are not approved in Australia for weight loss, but this was glossed over. Saying that ‘no one has applied to register it for treating obesity’ is insufficient justification for off-label use. The article seems to only consider positive news on drugs. For example, it says semaglutide ‘is under consideration by European authorities for the treatment of obesity’, but does not mention that marketing authorisation was refused for phentermine/topiramate due to safety concerns.

Despite the author acknowledging that there is no evidence base to support using a combination of drugs, several potential combination regimens are suggested on theoretical grounds. This is not in line with the evidence-based philosophy that underpins the work of NPS MedicineWise.

Conflicts of interest also call into question the independence of some recommendations. It is now recognised that pharmaceutical sponsorship may influence the reporting of trial results and recommendations made about medicines.

Andy Morgan
Senior lecturer
Liz Sturgiss
Senior research fellow
School of Primary and Allied Health Care, Monash University, Melbourne, Vic.

REFERENCES


Joseph Proietto AM, the author of the article, comments:

The need for medicines to maintain weight loss is based on the fact that nearly everyone regains weight after weight loss. I agree that there is a need to test these drugs for long-term safety. The problem is that regulatory authorities mandate that to register a drug to treat obesity it must show 5% weight loss. In fact, they should mandate safety studies with long-term use.

So far, we have a 3.8-year safety study showing that liraglutide improves cardiovascular outcomes in patients with type 2 diabetes. A two-year study of patients with diabetes and established cardiovascular disease showed that semaglutide once weekly reduced cardiovascular events.

Another two-year study concluded that a combination of phentermine and topiramate maintained weight loss and improved cardiovascular and metabolic variables and decreased rates of incident diabetes compared to placebo. A study to assess cardiovascular safety for naltrexone/bupropion was terminated early following an interim analysis after 25% and 50% of expected cardiovascular events had occurred. More research is needed, however the 25% and 50% data showed a mild reduction in events in the treatment group. Topiramate was mentioned because it is the only obesity drug that is cheap and thus affordable for most, and it was approved by the US Food and Drug Administration in combination with phentermine.
I am concerned by the ambiguity about progesterone/progestogen in the article ‘Hormonal contraception and mood disorders’.\(^1\) The summary correctly states ‘The link between oral contraceptive pills and depression relates to the amount and type of progestogen contained in these pills’, but the article subsequently says that progesterone can worsen mood symptoms. Plausible links are said to include progesterone augmentation of GABA-induced inhibition of glutamate transmission, and progesterone increasing the concentrations of monoamine oxidase, resulting in decreased serotonin concentrations. However, these links should be referring to progestogen rather than progesterone.

To my knowledge (and according to all the given references,) progesterone is neuroprotective, whereas progestogen is not. It is the progestogen in oral contraceptive pills that has been linked to depressive mood.

Joanne Lipinski
Pharmacist (non-practising) and Naturopath (practising), Ormond, Vic.

REFERENCES

Eveline Mu and Jayashri Kulkarni, the authors of the article, comment:

As we referenced in our paper\(^1\) – progestogens in oral contraceptive pills can contribute to the worsening of mood symptoms in susceptible women. This is evidenced by the worsening of mood symptoms in women who use progestogen-only forms of contraception such as the progestogen-only pill and the levonorgestrel intrauterine device.\(^2\)

Regarding endogenous progesterones, it is believed that women with premenstrual dysphoric disorder have an abnormal GABA response to changes in allopregnanolone levels (a metabolite of progesterone) across the menstrual cycle, contributing to negative mood symptoms.\(^3\) As more studies examine the role of allopregnanolone and its metabolite progesterone their neuroprotective effects may be clearer.

Lipinski is correct that the two terms were used interchangeably in the article. We agree that progestogens are more likely to be implicated in depressed mood, but as we learn more about progesterone, the impact of this endogenous hormone on mood is yet to be fully determined.
**Drospirenone and mood**

*Aust Prescr* 2022;45:116

https://doi.org/10.18773/austprescr.2022.048

I read with interest the article ‘Hormonal contraception and mood disorders’, but noted that it overlooked the 4 mg drospirenone 24/4 progestogen-only pill (Slinda). The article also did not consider the 20 microgram ethinylestradiol/3 mg drospirenone preparation which has an indication for treatment of premenstrual dysphoric disorder.

Perhaps the authors might consider that the benefits shown in their pilot study may be due to a 24/4 preparation (also noted in the studies referenced in reducing pill-free interval) as well as the active ingredient?

Andrew Zuschmann
Obstetrician and gynaecologist, Anaria, Miranda, NSW

Conflicts of interest: Dr Zuschmann has been a consultant to Bayer, Besins and MSD.

**REFERENCE**


Eveline Mu and Jayashri Kulkarni, the authors of the article, comment:

The 4 mg drospirenone preparation became available in Australia in October 2021 after we wrote the article.¹

For contraceptives containing drospirenone, a 2012 Cochrane meta-analysis tentatively described improvement in women with premenstrual dysphoric disorder, however there was a large placebo effect.² Our clinical experience with the 20 microgram ethinylestradiol/3 mg drospirenone preparation in women with premenstrual dysphoric disorder and (commonly) a trauma history is that the lower dose ethinylestradiol, compared to many other preparations, did not improve premenstrual dysphoric disorder as well as the combination of estradiol and nomegestrol.³

The estradiol and nomegestrol combination is effective because of its 24/4 regimen. As the proposed aetiology for mood disturbance is related to the cyclical shift in endogenous estrogen, having more estradiol (24 days) is better in terms of equilibrium of both mood and estrogen. Nomegestrol is a better progestogen in terms of neurotransmitter interactions. However, a head-to-head clinical trial of a 21/7 pill compared to 24/4 needs to be done to confirm this.

**REFERENCES**


Guidelines not for everyone

Aust Prescr 2022;45:117
https://doi.org/10.18773/austprescr.2022.049

I commend the editorial on electronic innovation in the implementation of clinical guidelines.1 While clinical guidelines ‘do not replace clinical judgement’ and ‘their application must be individualised to each patient, as they may not be appropriate for all patients’, the editorial highlighted that ‘only about half of all people with established cardiovascular disease are prescribed guideline-recommended treatments.’

What should be the expected rate of prescribed guideline-recommended treatments in a population? It varies with cultural, socioeconomic literacy rate and access to healthcare. Individuals have different outlooks or perceptions and consequently risk appetite which determines their actions. Others need time to deliberate on issues presented to them and may not decide immediately to take up offers of treatment. In shared decision-making, it is expected that some will not take up guideline-recommended treatment regardless of the quality of information provided. Given that compliance, defined as ‘the extent to which the patient’s behaviour matches the prescriber’s recommendations’,2 is nowadays regarded as paternalistic, expectations of near 100% uptake by patients of guideline-recommended treatment would be contentious and unrealistic. Most countries face similar issues in chronic conditions like cardiovascular diseases.3

Measuring the prescription rate of guideline-recommended treatment does not acknowledge any doctor–patient discussion which does not result in that treatment. This is particularly relevant if prescribing rates are used to judge the performance of health professionals regardless of electronic clinical decision support. Beyond guideline-recommended treatment uptake lies the matter of adherence previously discussed in Australian Prescriber.4 Both issues present similar challenges. Not achieving a high uptake or adherence to guideline-recommended treatment should not be attributed predominantly to the clinical practice of doctors.

Shyan Goh
Orthopaedic surgeon, Meadowbrook, Qld

REFERENCES

Jo-Anne Manski-Nankervis, the author of the editorial, comments:

I agree that we should not be aiming for 100% ‘compliance’ with guideline recommendations. Indeed, if that were obtained, there would undoubtedly be concern about overtreatment and failure to individualise therapies. In general practice, multimorbidity is the norm and so clinicians take into account a number of variables, including patient preference, when considering their prescribing decisions. Taking these factors into account though, a translation of guideline-recommended care of only 50% suggests that there are significant barriers which may be attributed to the guidelines themselves, as well as the health professional, health system and patient factors mentioned in the editorial. The inclusion of shared decision-making aids within guidelines will hopefully facilitate discussion between healthcare professionals and patients to bridge part of this gap.

The terminology of compliance and adherence is not a helpful driver of change. Language is powerful. The diabetes community has led this discussion, suggesting that these terms should be avoided.1 I think we also need to consider the use of these terms for our health professional colleagues. Ensuring that health professionals and the broader community have access to high-quality information including guidelines and shared decision-making aids is important. Facilitating health professionals to interrogate their data to explore their practice relative to others and focusing on appropriateness rather than compliance may also be helpful drivers to assist in reflection and ongoing optimisation of clinical practice. Setting a broad-brush target for guideline ‘concordance’ in fact may not be helpful and may even be harmful.

REFERENCE

The anticholinergic burden: from research to practice

**Summary**

Drugs with anticholinergic effects are known to cause adverse effects such as dry mouth, constipation and urinary retention. In older people drugs with anticholinergic effects may contribute to cognitive decline and a loss of functional capacity.

Many drugs that are not in the anticholinergic drug class also have anticholinergic effects. They include antidepressants, antipsychotics and antihistamines.

Taking multiple drugs with anticholinergic effects creates an anticholinergic burden. It is important that clinicians identify which patients are at risk. There are several tools to assess the anticholinergic burden.

Clinicians can use these tools to make a pharmacological risk assessment when reviewing a patient’s medicines. This can assist decisions about continuing or stopping drugs with anticholinergic effects.

Deprescribing drugs with anticholinergic effects has several potential benefits in older people. In addition to reversing adverse effects, deprescribing may prevent problems such as falls.

**Introduction**

Drugs that have anticholinergic effects block acetylcholine receptors in central or peripheral tissues. This cholinergic antagonism can either be an intended therapeutic effect or an unwanted adverse effect. In addition to drugs classified as anticholinergics, many other drugs have some anticholinergic effects. These include antidepressants, antipsychotics and antihistamines. Drugs with anticholinergic properties are commonly taken by older adults to treat conditions such as Parkinson’s disease, depression, pain, urinary incontinence and allergy. Evidence suggests that 20–50% of older adults are prescribed drugs with anticholinergic effects. Multiple drugs acting to block acetylcholine receptors will have cumulative effects, which can be described as the person’s anticholinergic burden.

The anticholinergic burden appears to be increasing. A recent UK study reported up to a ninefold increase in the anticholinergic burden over 25 years with increases in prescribing of most anticholinergic drug classes and in polypharmacy.

**Adverse effects**

Drugs with anticholinergic effects have a significant adverse-effect profile. Common anticholinergic adverse effects include dry mouth, urinary retention, constipation, cognitive decline and loss of the functional capacity to perform activities of daily living. Adverse anticholinergic effects are particularly problematic in older adults due to age-related changes in pharmacokinetic and pharmacodynamic processes, and the presence of multi-morbidity, polypharmacy and geriatric syndromes such as frailty. In older adults, the anticholinergic burden is linked with serious adverse effects including falls, functional decline, delirium and death. A recent Cochrane review suggests that older adults without cognitive impairment who are exposed to drugs with anticholinergic effects may be at an increased risk of cognitive decline and dementia. Furthermore, many drugs with anticholinergic effects may cause significant deterioration in the oral health of older adults.

**Assessing the anticholinergic burden**

At present, there is no universal way to assess the anticholinergic burden to inform clinical practice. Several tools have been developed to estimate the cumulative effects of drugs with anticholinergic effects in individuals. They are based on either expert consensus, serum anticholinergic activity or pharmacological principles.

Examples of tools to measure the anticholinergic burden include the Anticholinergic Drug Scale, Anticholinergic Cognitive Burden Scale and the Anticholinergic Risk Scale. The Drug Burden Index (DBI) is a measure of exposure to drugs with anticholinergic and sedative effects. However,
many of the drugs classified as sedative for calculation of the DBI are also included in other anticholinergic burden scales. The agreement between the various measures of anticholinergic burden is poor, with tools identifying different drugs as anticholinergic and giving them different weightings using different criteria. A barrier to the use of the tools for clinical risk assessment is the difficulty of calculating the anticholinergic burden during a consultation.

**Quality use of drugs with anticholinergic effects**

Measures of anticholinergic burden and the DBI can inform clinicians of the cumulative risk of adverse drug effects, including global effects on functional independence. The clinician can weigh up the risk of adverse events against the benefits of continuing the drug for an individual patient. This pharmacological risk assessment score differs conceptually from long expert consensus lists of ‘potentially inappropriate medications’, and the Screening Tool of Older Persons’ Prescriptions (STOPP) or the Screening Tool to Alert to Right Treatment (START), which consider evidence of both safety and efficacy in older populations.

If a clinician and a patient decide to continue a treatment with a drug with anticholinergic or sedative effects, there are several principles to consider.

1. Minimise the use of the anticholinergic or sedative drug.
   a. Optimise non-pharmacological management strategies for the condition being treated.
   b. Optimise treatment of the condition using drugs without anticholinergic or sedative effects.
   c. Use the minimum dose of the anticholinergic or sedative drug that is required to manage the condition for the shortest duration.

2. Proactively address the adverse effects of the anticholinergic or sedative drug, for example refer for exercise training to reduce falls and frailty.

3. Minimise exposure to other drugs that are contributing to the anticholinergic and sedative load. Review all of the person’s other drugs, including over-the-counter medicines, such as antihistamines.

4. Monitor the patient closely (and teach them to self-monitor) for efficacy and safety. Look for alternative treatments without anticholinergic or sedative effects. Review all drugs frequently.

5. If another drug with anticholinergic or sedative effects is needed subsequently, then revisit steps 1–4, with the aim of minimising the person’s total exposure to drugs with these effects.

**Deprescribing**

Tools like the DBI help identify the functional burden of drugs and provide a framework for shared decision making in prescribing and deprescribing. To calculate the DBI, registered Australian healthcare professionals can enter the patient’s drugs into G-MEDSS software. This will provide the patient’s total DBI score and the contribution of each of their drugs to that score.

The priorities for deprescribing depend on the treatment options, harms, benefits, patient preference and the complexity of drug withdrawal. Applying these criteria, it is often a priority to deprescribe antipsychotic drugs if possible, when they are being used to manage behavioural and psychological symptoms of dementia.

In practice, anticholinergic drug effects are difficult to differentiate from the effects of ageing and disease. However, it is important to differentiate adverse drug effects because they are often reversible with deprescribing. While studies aiming to reduce overall anticholinergic burden have only been powered to assess changes in drug use, there is evidence of clinical benefit from deprescribing some drug classes with anticholinergic or sedative effects. For example, falls can be reduced by withdrawing psychotropic drugs.

Considering the anticholinergic and sedative burden and the possibility of deprescribing are important parts of a comprehensive medication review of frail older people. Deprescribing anticholinergic and sedative drugs is feasible but often requires slow tapering to prevent withdrawal reactions. The discontinuation syndrome seen after abruptly stopping drugs with anticholinergic effects can include nausea, sweating, urinary urgency, orthostatic hypotension, tachycardia, anxiety and sleep disruption. Detailed guides on deprescribing drugs with anticholinergic and sedative effects are freely available to clinicians (see Box).

When discussing a trial of deprescribing sedative and anticholinergic drugs with a patient, it is helpful to consider the impact of adverse effects on what matters the most to that person. Most adverse

**Box Examples of deprescribing guides**

- NSW Therapeutic Advisory Group – Deprescribing tools
- Primary Health Tasmania – Deprescribing resources
- Canadian Deprescribing Network – Deprescribing guidelines and algorithms
The anticholinergic burden: from research to practice

Effects of anticholinergic and sedative drugs are multifactorial syndromes, such as falls, functional impairment, confusion, constipation, dry mouth or urinary retention. Drugs are the most reversible factors contributing to these syndromes. Reversing even one factor contributing to a geriatric syndrome can be enough to alleviate it. A medication review and trial of deprescribing may therefore improve successful ageing.

Conclusion

Many commonly prescribed drugs have anticholinergic effects. When a patient is taking several of these drugs, they may have a high anticholinergic burden. In older people this can lead to a loss of function and problems such as falls.

Several tools are available to assess the anticholinergic burden. These may assist clinicians when deciding if a patient’s treatment should be changed. There may be benefits from reducing the anticholinergic burden by deprescribing. 

Acknowledgment: Danijela Gnjidic is supported by the Australian National Health and Medical Research Council Dementia Leadership Fellowship.

Conflicts of interest: Sarah Hilmer developed and continues to lead an active research program on the Drug Burden Index. The Goal-directed Medication review Electronic Decision Support System (G-MEDSS), which includes a Drug Burden Index calculator, was developed by Lisa Kouladjian O’Donnell under the supervision of Sarah Hilmer, and is under consideration for commercialisation.

REFERENCES

SUMMARY

Sodium-glucose co-transporter 2 (SGLT2) inhibitors lower blood glucose by reducing the reabsorption of glucose in the kidney. They are a second-line therapy for type 2 diabetes.

During clinical trials it was noticed that SGLT2 inhibitors had favourable effects on cardiovascular and renal disease. This led to further trials that included patients without diabetes.

In studies of heart failure, SGLT2 inhibitors were beneficial in treating patients with a reduced left ventricular ejection fraction. A recent study has also reported benefits in patients with a preserved ejection fraction.

In chronic kidney disease, SGLT2 inhibitors may reduce disease progression. However, a decline in the glomerular filtration rate may be seen at the start of treatment.

As most experience with SGLT2 inhibitors is in diabetes, patients without diabetes need to be aware of why they are being prescribed these drugs. Some of the potential indications for SGLT2 inhibitors beyond diabetes are not yet approved by regulatory authorities.

Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors lower blood glucose and are an established second-line therapy in patients with type 2 diabetes. They increase glucose excretion by reducing its renal reabsorption. The drugs currently available in Australia are dapagliflozin, empagliflozin and ertugliflozin. Benefits beyond lowering glycated haemoglobin (HbA1c) have been reported in patients with type 2 diabetes who have multiple cardiovascular risk factors or established cardiovascular disease. Consistent reductions in hospitalisations due to heart failure and renal benefits have led to studies in patients with heart failure and chronic kidney disease. These have reported clear benefits regardless of the patient’s diabetes status. SGLT2 inhibitors therefore have an emerging role in the treatment of heart failure and chronic kidney disease. In some cases, these new indications have not yet been approved by the Therapeutic Goods Administration (TGA).

SGLT2 inhibitors in type 2 diabetes

Several SGLT2 inhibitors have been evaluated in cardiovascular outcome trials in patients with type 2 diabetes. They include empagliflozin, canagliflozin, dapagliflozin and ertugliflozin. A consistent finding in all these trials was a reduction in hospitalisation due to heart failure. A meta-analysis of placebo-controlled trials reported a 22% relative risk reduction in cardiovascular death or heart failure hospitalisation. In patients randomised to SGLT2 inhibitor therapy, there was also a 38% relative risk reduction in composite renal outcomes, comprising worsening estimated glomerular filtration rate (eGFR) or creatinine, end-stage kidney disease, kidney death or cardiovascular death.

SGLT2 inhibitors in heart failure

Heart failure can be classified according to left ventricular function. SGLT2 inhibitors have been studied in patients with reduced and preserved left ventricular ejection fraction.

Reduced ejection fraction

Two large randomised, double-blind, placebo-controlled trials have reported that SGLT2 inhibitors are beneficial for patients who have heart failure with a reduced left ventricular ejection fraction (40% or below), regardless of their diabetes status. The mechanism of this benefit is not fully understood. It may relate to the drug’s natriuretic effect, enhanced erythropoiesis, beneficial changes in cellular energetics or reversal of adverse ventricular remodelling.

The DAPA-HF trial reported a 26% relative risk reduction in cardiovascular death or worsening heart failure in patients randomised to receive dapagliflozin. The magnitude of benefit was similar irrespective of the patient’s background therapy for heart failure.

The EMPEROR-Reduced trial compared empagliflozin to placebo. It also found a significant relative reduction in cardiovascular death or heart failure.
Sodium-glucose co-transporter 2 inhibitors beyond diabetes

hospitalisation. The combined risk was 25% lower in patients given empagliflozin, mainly due to a lower risk of hospitalisation for heart failure.

Due to the results of these trials, both the American Heart Association/American College of Cardiology/Heart Failure Society of America and European Society of Cardiology heart failure guidelines have included SGLT2 inhibitors as first-line therapy for patients with heart failure and a reduced left ventricular ejection fraction.

Both dapagliflozin and empagliflozin are listed on the Pharmaceutical Benefits Scheme (PBS) for patients with heart failure with left ventricular ejection fraction less than or equal to 40%, who are receiving optimal standard chronic heart failure treatment, which must include a beta blocker and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor, unless contraindicated or cannot be tolerated.

Preserved ejection fraction

Patients who had heart failure with a preserved left ventricular ejection fraction were studied in the EMPEROR-Preserved trial. This reported a 21% relative risk reduction in the composite primary end point of cardiovascular death or heart failure hospitalisation in patients randomised to receive empagliflozin. This result was predominantly driven by a 29% relative risk reduction in heart failure hospitalisation. This is the first major outcome study of heart failure with a preserved left ventricular ejection fraction to show a benefit. The ongoing DELIVER study is evaluating the safety and efficacy of dapagliflozin in heart failure with a preserved left ventricular ejection fraction, with results expected in 2022.

The most recent American Heart Association/American College of Cardiology/Heart Failure Society of America heart failure guidelines recommend the use of SGLT2 inhibitors in patients with heart failure with a preserved ejection fraction to reduce heart failure hospitalisations and cardiovascular mortality.

SGLT2 inhibitors in chronic kidney disease

The reported improvements in renal function with SGLT2 inhibitors probably relate at least partly to reduced intraglomerular pressure, but the mechanism of action remains an active area of investigation. The improved renal outcomes seen in patients with diabetes led to trials specifically investigating renal end points.

The DAPA-CKD trial studied patients with chronic kidney disease with or without type 2 diabetes (67.5% had diabetes). They had an eGFR of 25–75 mL/minute/1.73 m² and a urinary albumin/creatinine ratio (mg/g) of 200–5000. Compared with placebo, dapagliflozin led to a 39% reduction in the relative risk for a sustained fall in eGFR, end-stage kidney disease or death from cardiovascular or renal causes. The benefits were similar in patients with and without diabetes. Recently, dapagliflozin has been approved by the TGA to reduce the progression of proteinuric chronic kidney disease, however this indication is not listed on the PBS. The ongoing EMPA-KIDNEY trial is studying the effect of empagliflozin on cardiovascular and renal outcomes in patients with chronic kidney disease.

SGLT2 inhibitor prescribing

The SGLT2 inhibitors are generally well tolerated and the process of prescribing these drugs is relatively uncomplicated compared to other treatments for heart failure, with no requirement for dose titration in the majority of patients. SGLT2 inhibitors should not be used in patients with type 1 diabetes due to a significant increased risk of ketoacidosis. They should also not be used in patients who are pregnant or lactating or in patients requiring dialysis.

While most of the safety data were derived from patients with type 2 diabetes, recent studies that included patients without diabetes have reported a favourable safety profile. Indeed, there were no reported cases of ketoacidosis in the patients without diabetes enrolled in the DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved and DAPA-CKD studies. Postmarketing follow-up continues to be necessary as adverse drug reactions are often detected and these should be reported to the TGA.

A reduction in systolic blood pressure due to volume depletion may be observed, which may require a reduction in diuretic dosing provided there is no clinical evidence of congestion.

Considerations before prescribing

There are adverse effects and comorbidities to consider before starting SGLT2 inhibitors (Table). Renal function

A transient reduction in renal function is common when starting SGLT2 inhibitors due to their mechanism of action, but is not a reason to stop therapy, unless the decline progresses. Recheck renal function to confirm that this acute deterioration is not continuing.

Ketoacidosis

Ketoacidosis is uncommon, but life-threatening. SGLT2 inhibitors should not be used in patients with a history of ketoacidosis, unless under specialist supervision. It is more likely in patients with diabetes, or during periods of acute illness or fasting (peri-procedural fasting, bowel preparation,
Table  Adverse effects of sodium-glucose co-transporter 2 inhibitors

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Practice point</th>
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<tbody>
<tr>
<td><strong>Genitourinary infections</strong></td>
<td>Patient education: perineal hygiene and advice on signs and symptoms of urinary or genital infection, including fever and pain, tenderness or swelling in the genital area. Prompt assessment and treatment to avoid more serious systemic infections, including Fournier’s gangrene and necrotising fasciitis, urosepsis and pyelonephritis.</td>
</tr>
<tr>
<td>Increased risk of mycotic infections. Candida vaginitis in women, balanitis in men (common &gt;1%). Urinary tract infections (largely non-severe and resolve quickly, common &gt;1%). Cases of necrotising fasciitis of the perineum (Fournier’s gangrene) have been reported (rare &lt;0.1%).</td>
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<tr>
<td><strong>Ketoacidosis</strong></td>
<td>Patient education regarding symptom monitoring and the importance of temporary cessation during periods of acute illness or fasting. Provide written sick-day plan. Refer to local guidelines regarding peri-procedural management. For example, Periprocedural Diabetic Ketoacidosis (DKA) with SGLT2 Inhibitor Use (Alert Update September 2020).</td>
</tr>
<tr>
<td>Postmarketing studies have reported an increased risk of ketoacidosis, especially during periods of acute illness or fasting (i.e. peri-procedural fasting, bowel preparation, low carbohydrate diet, excess alcohol consumption, vomiting or diarrhoeal illnesses) and reductions in insulin dose. Ketoacidosis is rare (&lt;0.1%) but can be life-threatening. It may occur even in the absence of elevated blood glucose.</td>
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<tr>
<td><strong>Volume depletion/renal function</strong></td>
<td>Assess volume status and renal function at baseline. May require adjustment of baseline diuretic therapy. May reduce systolic blood pressure. Consider monitoring of renal function in at-risk patients.</td>
</tr>
<tr>
<td>Volume depletion may occur due to a natriuretic and diuretic effect (infrequent 0.1-1%). Temporary decline in renal function is due to tubuloglomerular feedback (common &gt;1%).</td>
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<tr>
<td><strong>Hypoglycaemia</strong></td>
<td>May require dose reduction of insulin and sulfonylureas.</td>
</tr>
<tr>
<td>Risk is increased if co-prescribed sulfonylureas or insulin, or there is a history of frequent hypoglycaemic episodes (common &gt;1%).</td>
<td></td>
</tr>
<tr>
<td><strong>Fracture risk</strong></td>
<td>Assess harm versus benefit before prescribing.</td>
</tr>
<tr>
<td>An increased incidence of fractures was observed in a trial of canagliflozin (not available in Australia) in patients with type 2 diabetes and a high cardiovascular risk. However, these findings have not been observed in other studies evaluating the safety of SGLT2 inhibitors.</td>
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<tr>
<td><strong>Lower limb amputation</strong></td>
<td>Patient education regarding preventive foot care.</td>
</tr>
<tr>
<td>An increased incidence of lower limb amputations was observed in a trial of canagliflozin (not available in Australia) in patients with type 2 diabetes and a high cardiovascular risk. However, these findings have not been observed in other studies evaluating the safety of SGLT2 inhibitors.</td>
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<td>Source: adapted from reference 11</td>
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</table>

low carbohydrate diet, excess alcohol consumption, vomiting or diarrhoeal illnesses) and following reductions in insulin dose. Ensure a written plan about managing sick days is provided to all patients. While there are no specific sick-day plans for heart failure, the principles are similar to those used in diabetes. Consider ketoacidosis in patients taking SGLT2 inhibitors who present with signs and symptoms of metabolic acidosis, even if their blood glucose is not elevated.

Urogenital infections
While urinary tract infections are listed as adverse effects of SGLT2 inhibitors, recent randomised control trials have not reported a significant excess risk compared to placebo. Treat promptly if patients present with signs and symptoms of urinary tract infections to reduce the risk of progression to urosepsis or pyelonephritis.

Fungal genital infections are more likely in patients treated with SGLT2 inhibitors and occur more commonly in women. These infections are usually mild.

Cases of necrotising fasciitis of the perineum (Fournier’s gangrene) have been reported. Patients who present with pain, tenderness, erythema or swelling in the genital or perineal area should be urgently examined. Necrotising fasciitis is a medical emergency.
Sodium-glucose co-transporter 2 inhibitors beyond diabetes

Conclusion

In Australia, the uptake of SGLT2 inhibitors to treat patients with non-diabetic indications is evolving as it appears the benefits extend beyond glucose lowering. Their role in medical therapy for heart failure with either reduced or preserved left ventricular ejection fraction has been recognised in international guidelines, regardless of the patient’s diabetes status. Given the results of the DAPA-CKD study, it is likely that future guidelines will also recommend SGLT2 inhibitors in patients with proteinuric chronic kidney disease.

REFERENCES


FURTHER READING


The adverse effects of SGLT2 inhibitors are mainly known from studies in diabetes. Patients without diabetes will need advice on how the drugs are used in other conditions. ◊

Conflicts of interest: John Atherton has been a member of advisory boards and received honoraria and travel support to attend conferences and educational meetings from AstraZeneca, Boehringer Ingelheim and Eli Lilly.
How to step down asthma preventer treatment in patients with well-controlled asthma – more is not always better

SUMMARY
Most of the benefit of asthma preventer inhalers is seen with low doses. However, many Australian patients are prescribed doses of inhaled corticosteroids that are higher than necessary to control their asthma.

Prescribing unnecessarily high preventer doses increases the patient’s risk of adverse effects. They may also increase the patient’s out-of-pocket costs.

Asthma guidelines recommend considering a step-down in preventer treatment after asthma has been well controlled for two to three months in adults and for six months in children. The step-down process should be individualised for each patient.

Preventive therapy should not be stopped completely.

Introduction
Asthma management is not a case of ‘one size fits all’. A key goal is to customise treatment for the needs of each patient. This involves finding the lowest dose that will keep asthma symptoms well controlled and reduce the risk of severe attacks (also called severe flare-ups or exacerbations), while minimising the risk of adverse effects.

Inhaled corticosteroids
Australian asthma guidelines recommend that most adult and adolescent patients should be prescribed a low-dose inhaled corticosteroid (ICS) or an as-needed combination of low-dose ICS and low-dose formoterol. Only some patients need daily treatment with a combination of low-dose ICS with a long-acting beta, agonist (LABA). Few patients require high doses of the ICS–LABA combination, or add-on treatment (for ICS doses for adults and adolescents, see Table 1). For children 6–11 years, regular ICS is recommended for those who have symptoms more than once weekly, or frequent or moderately severe exacerbations. Few children require high doses (for ICS doses for children, see Table 2). Guidelines recommend the consideration of stepping down the dose of therapy when asthma has been stable and well controlled for 2–3 months in adults, and six months in children.

Despite these guidelines, a recent study found that 71% of Australian adults and adolescents with asthma who were prescribed preventer inhalers had been dispensed a high-dose combination of ICS–LABA. There are several possible explanations for this deviation from the recommendations. Some patients with frequent symptoms at diagnosis may have been prescribed a high-dose preventer, without the dose being reviewed after the symptoms improved. Many patients have their preventer dose increased during a flare-up, but few return for review after they have recovered, so they remain indefinitely on unnecessarily high doses. In some cases, clinicians, given the substantial pressures on their time, feel that switching asthma treatment may not be a worthwhile use of their time, especially if there is a risk that asthma control will be worse after the switch.

Why consider stepping down asthma treatment?
Most of the benefits of ICSs are achieved with low doses which are associated with very little risk of adverse effects. Long-term treatment with high doses is associated with a small increase in the background risk of conditions such as cataract and osteoporosis.

Some patients are concerned about any type of corticosteroid treatment, with some concerns mistakenly driven by information about anabolic steroids. Patients may not be aware that the risks described in Consumer Medicines Information are seen only with high ICS doses taken for a long period of time, or with oral corticosteroids. When starting treatment, prescribers should emphasise to the patient that one of the goals of asthma management is to first achieve good control and then find the lowest dose for them that will keep the asthma well controlled.
An additional reason for considering stepping down the dose is that it may substantially reduce out-of-pocket costs for patients. This may improve their adherence to therapy.9,10

Which patients should be considered for a step-down?

Evidence shows that preventer treatment can be stepped down safely. Systematic reviews of studies in properly selected patients found no overall increase in the risk of exacerbations.11 However, the dose of ICS that will keep asthma well controlled varies between patients, so consider each step-down as a treatment trial and monitor the patient closely afterwards. There is much less evidence about stepping down treatment in children.11

Consider stepping down therapy when asthma has been well controlled by a stable dose of ICS or ICS–LABA for at least 2–3 months in adults and adolescents and after six months in children, particularly if the ICS dose is medium or high by age group (see Tables 1 and 2).1,2 All patients should have a written asthma action plan before starting a step-down.

To assess symptom control, use a tool such as the Asthma Control Test. This evaluates symptoms, reliever use and perceived control over four weeks.12 Also ask patients if they have had any flare-ups in the last 12 months, as these increase the risk of future exacerbations. A flare-up more than three months ago that was triggered by an isolated upper respiratory infection would not necessarily be a contraindication to stepping down the dose, provided symptoms had been well controlled since then.

Poor adherence is not necessarily a barrier to stepping down, provided the patient has well-controlled asthma and no exacerbations. A greater reduction in the prescribed dose may be considered if the patient has been using their preventer infrequently. However, if a patient notices more symptoms after missing only one or two doses of their current preventer, they are likely to need their current dose, so it should not be reduced.

During pregnancy, consider stepping down only if the woman has well-controlled asthma and is taking a high-dose preventer. Otherwise, postpone stepping down until after delivery.13

Stepping down in patients with severe asthma

For patients with severe asthma, careful step-down of inhaled therapy can be considered if symptom control and exacerbations respond to add-on biologic therapy such as benralizumab, dupilumab, mepolizumab or omalizumab. The highest priority is to gradually reduce and stop oral corticosteroids. Reducing the ICS dose can be considered after 3–6 months, but not to below a medium dose.11 In severe asthma, any dose reduction should be in consultation with a specialist.

A step-by-step guide to stepping down

Depending on the patient’s current therapy, there are several step-down options (see Table 3). The step-down process is individualised for each patient.
### Table 3  Step-down options for preventer therapy in adults and adolescents who have had well-controlled asthma for at least 2–3 months

<table>
<thead>
<tr>
<th>Treatment level</th>
<th>Current preventer treatment</th>
<th>Suggested step-down options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5</strong></td>
<td>High-dose combination ICS–LABA plus add-on therapy such as biologic therapy or oral corticosteroids for severe asthma</td>
<td>Discuss with the specialist who prescribed the add-on treatment. Once asthma is well controlled, the highest priority for stepping down is to gradually reduce and then cease oral corticosteroids (if prescribed); check for adrenal suppression. Advise patients not to stop their combination ICS–LABA treatment. Do not reduce ICS–LABA below a medium dose.</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>Medium- or high-dose ICS–LABA–LAMA maintenance, plus as-needed SABA</td>
<td>Consider ceasing the LAMA, and continuing the same dose of ICS–LABA. OR If the ICS dose is high, consider reducing to a medium dose (but not to low dose) while continuing LAMA.</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>Medium-dose MART, i.e. 2 inhalations twice daily of budesonide/formoterol 200/6 micrograms or beclometasone/formoterol 100/6 micrograms, plus 1 inhalation taken as needed for symptom relief</td>
<td>Low-dose MART, i.e. 1 inhalation twice daily of budesonide/formoterol 200/6 micrograms or beclometasone/formoterol 100/6 micrograms, plus 1 inhalation taken as needed for symptom relief.</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Medium- or high-dose ICS–LABA maintenance, plus as-needed SABA</td>
<td>Continue ICS-LABA, reducing the ICS dose by 25–50% by: • prescribing a lower dose ICS-LABA formulation OR • for ICS-LABA combinations prescribed more than once daily, by reducing the number of inhalations per day.</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Low-dose MART, 1 inhalation twice daily of budesonide/formoterol 200/6 micrograms or beclometasone/formoterol 100/6 micrograms, plus 1 inhalation taken as needed for symptom relief</td>
<td>As-needed only low-dose budesonide/formoterol 200/6 micrograms. [Note: as-needed only treatment has not been studied with beclometasone/formoterol]</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Low-dose fluticasone furoate vilanterol (a once-daily ICS-LABA) plus as-needed SABA</td>
<td>Consider stepping down to once-daily fluticasone furoate (ICS alone) plus as-needed SABA.</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Low-dose combination ICS-LABA maintenance (twice-daily formulations), plus as-needed SABA</td>
<td>Reduce ICS-LABA dose by 25–50% by: • reducing from twice-daily to once-daily OR • for patients prescribed 2 puffs per dose, reducing to 1 puff per dose.</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Maintenance low-dose ICS plus as-needed SABA</td>
<td>Continue daily low-dose ICS (with a lower dose if available), plus as-needed SABA.</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>As-needed low-dose budesonide/formoterol 200/6 micrograms taken as needed for symptom relief</td>
<td>Reduce to as-needed low-dose budesonide/formoterol 100/6 micrograms per dose.</td>
</tr>
<tr>
<td><strong>1</strong></td>
<td>As-needed SABA alone (not a preventer)</td>
<td>SABA-only treatment is not recommended, except for the very few patients who have symptoms less than twice a month and no risk factors for exacerbations.</td>
</tr>
</tbody>
</table>

Treatment levels in the table correspond to Australian asthma guidelines for adults and adolescents.1

**ICS** inhaled corticosteroid

**LABA** long-acting beta, agonist

**LAMA** long-acting muscarinic antagonist, as separate inhaler or in triple ICS–LABA–LAMA combination

**MART** maintenance and reliever therapy with budesonide/formoterol or beclometasone/formoterol. In this regimen, the patient takes ICS/formoterol combination as both their maintenance treatment and as their reliever (instead of a SABA)

**SABA** short-acting beta, agonist
How to step down asthma preventer treatment in patients with well-controlled asthma – more is not always better

Use shared decision making
Explain the rationale and the process for stepping down the dose, and understand the patient’s or parent’s willingness or concerns. Discuss how the dose required for the prevention of flare-ups will be individualised for them.

Timing
Choose an appropriate time to reduce the dose. For example, do not step down if the patient is developing a cold, or about to travel, or just before a holiday period. For patients who are allergic to rye grass and live in an area where thunderstorm asthma may occur, it would not be advisable to step down their treatment during the pollen season. Step down before the previous inhaler is completely empty, so the patient can resume their previous dose promptly if asthma worsens.

Assess the patient’s risk factors
Risk factors include a history of previous exacerbations and allergen exposure in sensitised patients.

Record the patient’s baseline asthma status
Use the Asthma Control Test or document how many days each week the patient has asthma symptoms, or needs to use their inhaler to relieve symptoms. Document lung function if available.

Make small dose adjustments gradually
The ICS dose can be reduced by 25–50%, by prescribing a lower dose formulation or reducing the frequency of use. Consider reducing in two steps of 25% rather than a single 50% reduction. For example, if the patient is taking two puffs twice a day, suggest they drop one of the evening puffs. If they remain stable after one month, drop the other evening dose so they would then be taking two puffs once a day.

Self-monitoring
Ask the patient to monitor symptoms and reliever use, and record the date of the step-down in their diary or calendar. Advise them that if, over a few weeks, they experience an overall increase in symptoms or reliever use, or start waking at night due to asthma, they should resume their previous dose. For patients who are anxious, or about whom one is concerned, consider asking for two weeks of peak expiratory flow monitoring as a baseline, then mark the step-down date and continue recording for another 3–4 weeks. The Woolcock peak flow chart makes it easy to detect exacerbations and gradual changes. Monitoring peak expiratory flow is particularly useful given reduced access to spirometry during the COVID-19 pandemic. The National Asthma Council has information to assist with self-monitoring.

Action plan
Make sure the patient’s written asthma action plan is up to date, so that they know what to do and who to contact if they have a flare-up.

Review
Book a follow-up visit for two or three months after stepping down (or earlier if there is concern) and prompt the patient to contact their GP sooner if their asthma worsens. At the follow-up visit, assess symptom control, adherence, reliever use and lung function (if test available). If the patient’s asthma is still stable, consider stepping down by another 25–50%.

Do not completely stop inhaled corticosteroids
In adults or adolescents, completely stopping preventive therapy increases the risk of severe exacerbations.

New step-down options in mild asthma
For adults and adolescents with well-controlled asthma on a low-dose ICS or low-dose ICS–LABA, with an as-needed short-acting beta2 agonist (SABA) reliever, one option is to continue daily treatment indefinitely. However, patients with few symptoms are often poorly adherent to therapy, increasing their risk of severe exacerbations.

A new step-down option available in Australia since 2020 is to switch to an as-needed combination of low-dose budesonide with formoterol. The patient uses the low-dose budesonide/formoterol inhaler whenever needed for symptom relief, instead of a SABA. This option is supported by three large studies including step-down in mild asthma, that showed symptom control and lung function were similar, and the risk of severe exacerbations was the same or lower, compared with continuing regular daily ICS with as-needed SABA. Importantly, the risk of severe exacerbations was reduced by more than 60% compared with switching to SABA-only treatment. Patients took an average of three to four doses of budesonide/formoterol 200/6 micrograms per week, so in clinical practice, one inhaler would last an average of six months. Although the initial out-of-pocket cost to the patient would be higher, the average daily cost to the patient over the life of the inhaler would be much lower than with daily ICS or daily ICS–LABA, plus an as-needed SABA.

Smaller studies in adults and children have found that it is possible to step down from daily ICS to
taking low-dose ICS only when the patient takes their SABA for symptom relief. This is more effective than SABA alone at preventing exacerbations.2,21 This approach is not currently recommended in Australian asthma guidelines.

**Conclusion**

A key goal of asthma management is to customise the treatment to the patient’s needs, by first achieving good asthma control and then finding the minimum effective dose that, together with an asthma action plan, will minimise the patient’s risk of severe exacerbations. This approach optimises the benefit for patients, reduces the risk of adverse effects, and reduces costs for the patient and the healthcare system. With shared decision-making and a careful plan, many patients are keen to engage in the process of optimising their asthma management.<ref>

**REFERENCES**


Conflicts of interest:

In the last three years, Helen Reddel’s institute has received independent research funding from AstraZeneca, GlaxoSmithKline and Novartis. She or her institute has received honoraria for participation in advisory boards for AstraZeneca, Chiesi, GlaxoSmithKline, Novartis and Sanofi-Genzyme; honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Sanofi-Genzyme and Teva for independent medical educational presentations; consulting fees from AstraZeneca and Novartis. Helen Reddel is Chair of the Global Initiative for Asthma (GINA) Science Committee, and a member of the Australian Asthma Handbook Guidelines Committee.

In the last three years, Gloria Foxley’s institute has received independent research funding from AstraZeneca, GlaxoSmithKline and Novartis.

In the last three years, Sharon R Davis’s institute has received independent research funding from AstraZeneca, GlaxoSmithKline and Novartis.

Full text free online at nps.org.au/australian-prescriber
Severe adverse drug reaction to allopurinol

Case

A 72-year-old Vietnamese man presented to hospital with a widespread rash, hypotension and diarrhoea. The patient had a history of hypertension treated with olmesartan for the past two years. Four weeks before presentation he had started allopurinol 300 mg daily for asymptomatic hyperuricaemia. Ten days after starting allopurinol the patient had noticed a pruritic erythematous rash on the abdomen, but was advised to continue allopurinol.

On examination the patient was febrile and hypotensive. He had a widespread morbilliform rash that spared the palms and soles. There were no mucosal lesions. Pathology testing revealed an acute kidney injury (creatinine 214 micromol/L, (baseline 130 micromol/L two years earlier)), liver injury (alanine transaminase 224 U/L and aspartate transaminase 224 U/L) and eosinophilia (peaking at 3.34 × 10³/L five days after admission) with reactive lymphocytes on the blood film. The diagnosis on admission was drug reaction with eosinophilia and systemic symptoms (DRESS).

The patient was treated with high-dose corticosteroids (50 mg prednisolone for one week then reducing by 10 mg every two days until finished) and intravenous fluids. He improved over the following days, but kidney function was slow to recover and his liver function worsened before improving. The patient’s rash also improved and he was discharged after five days. Allopurinol was not resumed.

As DRESS was suspected, he had HLA typing. This revealed HLA-B*58:01.

Comments

Adverse drug reactions can range from mild cutaneous reactions to very severe multisystem reactions that can be life-threatening. DRESS is a T-cell-mediated adverse drug reaction characterised by widespread rash with or without eosinophilia, fevers, lymphadenopathy and organ involvement (most commonly kidney or liver injury). It is a life-threatening condition with a mortality of 10%. The diagnosis is clinical, but the RegiSCAR score may be useful in considering the likelihood of DRESS.¹

Human leukocyte antigens (HLAs), also known as the major histocompatibility complex, are central to immune function. They are involved in DRESS. There is widespread T-cell activation as a result of a drug altering the interaction between antigen-presenting cells and T cells.²

The most common drugs that induce DRESS are antibiotics (particularly beta lactams, sulfonamides and vancomycin), aromatic amine anticonvulsants and allopurinol.¹ The HLA alleles that predispose individuals to these T-cell-mediated reactions are common in particular ethnic groups so screening before prescribing these drugs has the potential to prevent life-threatening reactions.³

Identifying the culprit drug can be problematic in patients receiving multiple medicines. Often identification comes down to the temporal relationship between the drug and the reaction (usually 2–3 weeks after starting the drug), the prescription of known high-risk drugs and HLA typing when appropriate.

The culprit drug should never be prescribed again as future reactions may be more severe or fatal. Even small doses can precipitate another reaction so desensitisation is contraindicated.

Conclusion

DRESS is a potentially life-threatening adverse drug reaction. It occurs most commonly in association with particular drugs. In some cases, DRESS is associated with HLA alleles that are more common in some ethnic groups.

Allopurinol-induced DRESS is highly associated with the HLA class I allele HLA-B*58:01 which is of significantly higher prevalence in individuals of Asian descent. The risk of DRESS can be reduced by checking if these patients have HLA-B*58:01 and avoiding the drug in those who carry the allele.³ The American College of Rheumatology guidelines also recommend screening African-American patients. No screening is required in patients of other ethnic or racial backgrounds.⁴

Patients should always be counselled on the risk of DRESS with allopurinol, particularly in the first eight weeks of treatment. They should stop the drug immediately and see their GP at the onset of symptoms. Allopurinol should be started at low doses (no more than 100 mg/day), especially in those with chronic kidney disease, then slowly titrated according to target serum urate concentrations.⁴
REFERENCES


FURTHER READING

New drugs

Bimekizumab

**Approved indication: plaque psoriasis**

**Bimzelx (UCB Australia)**

pre-filled syringes or pens containing 160 mg/mL solution for injection

High concentrations of interleukin (IL)-17A, IL-17F and IL-17AF are involved in inflammation and the development of plaque psoriasis. Cytokine modulators, such as ixekizumab and secukinumab, have therefore been used as systemic treatments for psoriasis. These do not always result in rapid and sustained skin clearance, so a treatment is needed to achieve complete skin clearance quickly. Bimekizumab is a humanised monoclonal (IgG1) antibody designed to inhibit both IL-17A and IL-17F on the outer layer of the skin. The drug is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Bimekizumab is given as two subcutaneous injections of 160 mg each, once every four weeks to week 16 and once every eight weeks thereafter. In patients with a body weight of 120 kg or more, continuing with a four-weekly dose may need to be considered. Suitable injection sites include the thighs, abdomen and upper arms. The sites should be rotated. Injections must not be given into psoriasis plaques or skin that is tender, bruised, erythematous or indurated.

Steady state is reached at approximately 16 weeks with four-weekly dosing. Bimekizumab is likely to be metabolised into small peptides and amino acids via catabolic pathways like other immunoglobulins, so adverse interactions with drugs metabolised by the CYP450 system are not expected. The mean terminal elimination half-life is 23 days.

The safety and efficacy of bimekizumab have been studied in four multicentre, double-blind, phase III trials (Table):

- **BE-VIVID**: placebo and ustekinumab, an IL-12/23 inhibitor
- **BE-READY**: placebo
- **BE-SURE**: adalimumab, a tumour necrosis factor inhibitor
- **BE-RADIANT**: secukinumab, an IL-17A inhibitor.

These trials all included patients with moderate to severe psoriasis, defined by a Psoriasis Area and Severity Index (PASI) score of at least 12 (range 0–72, with higher scores indicating worse disease), at least 10% body surface area affected by psoriasis, and an Investigator’s Global Assessment score of at least 3 on a 5-point scale (with 0 representing complete clearance and 4 representing severe

<table>
<thead>
<tr>
<th>Table</th>
<th>Efficacy of bimekizumab in patients with moderate to severe plaque psoriasis</th>
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<tbody>
<tr>
<td><strong>Trial (duration)</strong></td>
<td><strong>Treatment arm</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>BE-VIVID1 (52 weeks)</td>
<td>Bimekizumab</td>
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<tr>
<td></td>
<td>Ustekinumab</td>
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<tr>
<td></td>
<td>Placebo</td>
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<tr>
<td>BE-READY2 (56 weeks)</td>
<td>Bimekizumab</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>BE-SURE3 (56 weeks)</td>
<td>Bimekizumab</td>
</tr>
<tr>
<td></td>
<td>Adalimumab</td>
</tr>
<tr>
<td>BE-RADIANT4 (48 weeks)</td>
<td>Bimekizumab</td>
</tr>
<tr>
<td></td>
<td>Secukinumab</td>
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</tbody>
</table>

* PASI 90 response: 90% or greater improvement from baseline in the PASI score
† PASI 100 response: 100% improvement from baseline in the PASI score (i.e. complete skin clearance)
psoriasis). Although the patients were followed up for 48–56 weeks, the efficacy end points were assessed at week 16 in these trials. Bimekizumab led to significant improvements in disease activity in all the trials. The improvements in the PASI score compared to baseline were sustained to the end of each study period.1–4 The efficacy of bimekizumab in patients with renal or hepatic impairment is unknown, as these populations were absent from the trials.

The rates of treatment-related discontinuation and death were low and similar across the different treatment and placebo arms.1–4 The most common treatment-emergent adverse events were oral candidiasis, upper respiratory tract infections, urinary tract infections, hypertension and diarrhoea.1–4 Cardiovascular events were reported in a small number of patients with pre-existing cardiovascular risk factors receiving bimekizumab in the BE-VIVID and BE-READY trials.1,2 Bimekizumab can increase the risk of infections such as respiratory tract infections and oral candidiasis. Treatment must not be continued in patients with an active infection until the infection resolves. Bimekizumab should be given with caution in patients with a history of recurrent infection or tuberculosis. New onset of ulcerative colitis was observed in the BE-VIVID and BE-RADIANT trials.1,4 Injection-site reactions were also reported. As with all therapeutic proteins, immunogenicity may occur. However, there has been no evidence of changes in efficacy or safety associated with the development of anti-bimekizumab or neutralising antibodies. The effect of bimekizumab on fertility is unknown. The treatment is not recommended in pregnant and breastfeeding women due to a lack of safety and efficacy data.

The dual-action mechanism of inhibiting both IL-17A and IL-17F with bimekizumab is effective and well tolerated in adult patients with plaque psoriasis. Further studies are needed to determine the sustainability of skin clearance achieved with bimekizumab beyond 56 weeks of treatment.

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 European Medicines Agency.

REFERENCES

**Cabotegravir**

**Approved indication:** HIV  
(Viiv Healthcare)  
30 mg film-coated tablets (Vocabria)  
vials containing 200 mg/mL suspension (Cabenuva)

Adherence to therapy is vital for viral suppression in people living with HIV. Therapy is lifelong so there is a need for regimens that are easy to adhere to and well tolerated. Early regimens had a high pill burden and current combination regimens still require daily doses. A longer acting drug that requires less frequent dosing may therefore help with adherence.

Cabotegravir is an analogue of dolutegravir, an integrase inhibitor. By binding to HIV integrase, cabotegravir blocks viral replication. To maintain viral suppression, cabotegravir is given with rilpivirine, a non-nucleoside reverse transcriptase inhibitor which has been available for many years. Both drugs can be formulated for oral or intramuscular administration.

Following injection into gluteal muscle, cabotegravir is slowly absorbed into the circulation. It can remain in the plasma for at least a year after a single injection. The mean half-life of intramuscular cabotegravir is 5.6–11.5 weeks with most of the dose being metabolised, mainly by uridine diphosphate glucuronosyltransferase 1A1. Although patients with severe impairment have not been studied, no dose adjustments are recommended for patients with liver or renal impairment.

The intramuscular formulation of rilpivirine is also slowly absorbed from the gluteal muscle. It is metabolised, mainly by cytochrome P450 3A, and has a mean half-life of 13–28 weeks. Like cabotegravir most of the dose is excreted in the faeces.

Cabotegravir and rilpivirine have many possible interactions with other drugs. Some are potentially serious and therefore the combination is contraindicated with anticonvulsants, antimycobacterial drugs, glucocorticoids and St John’s wort.

An open-label phase II trial (LATTE-2) investigated whether injections of cabotegravir and rilpivirine were as effective as oral cabotegravir with abacavir and lamivudine in suppressing HIV in previously untreated adults. All patients took the oral regimen for 20 weeks. A total of 286 patients then entered a maintenance period in which they were randomised to receive injections of cabotegravir and rilpivirine every four or eight weeks, or to continue the oral regimen. After 32 weeks of maintenance therapy, the plasma concentration of HIV RNA was below 50 copies/mL in most patients. This viral suppression was achieved by 94% (108/115) of the patients injected every four weeks and 95% (109/115) of those given a higher dose every eight weeks. The virus was suppressed in 91% (51/56) of the patients taking oral maintenance therapy. After 96 weeks of maintenance there was viral suppression in 87% of the four-weekly injection group and 94% of the eight-weekly injection group compared with 84% of the oral group.

Previously untreated patients were also studied in the subsequent open-label, phase III FLAIR trial. After a 20-week oral induction period, 283 patients were randomised to long-acting therapy while 283 continued oral therapy with dolutegravir, abacavir and lamivudine. Long-acting therapy began with four weeks of oral cabotegravir and rilpivirine. The patients were then given loading doses of the two drugs, followed by monthly maintenance doses. At 48 weeks after randomisation the viral RNA concentration was below 50 copies/mL in 93.6% of the patients receiving monthly injections and 93.3% of the oral maintenance group.

The phase III ATLAS trial enrolled patients who were already being treated with antiretroviral drugs. This open-label trial randomised 308 patients to continue their usual oral treatment and 308 to switch to long-acting therapy. This regimen began with four weeks of oral cabotegravir and rilpivirine followed by a loading dose and then monthly injections. After 48 weeks of the maintenance regimen 92.5% of the patients had less than 50 copies/mL. This concentration of viral RNA was also present in 95.5% of those who continued oral treatment.

Patients completing the ATLAS trial could enrol in the ATLAS-2M trial along with other previously treated patients. This open-label phase III trial compared monthly injections with higher doses given every eight weeks. After 48 weeks of therapy viral RNA had been suppressed below 50 copies/mL in 93% (489/523) of the patients injected monthly and 94% (492/522) of the patients injected every eight weeks.

Long-acting therapy can have long-lasting adverse effects. This is why the regimen begins with at least 28 days of oral therapy to assess if the patient can tolerate cabotegravir and rilpivirine. When intramuscular administration begins, the two drugs should be given at separate sites. Most patients will experience injection-site reactions with some developing a fever. Other common adverse events in the trials included headache, diarrhoea, nausea, back pain and upper respiratory tract infections.

The incidence of adverse effects was similar for the four-week and eight-week regimens with 2% of the patients in each group discontinuing because of adverse events. Liver function should be monitored...
as some patients may develop hepatitis. Patients with viral hepatitis were excluded from the trials. There has also been no study of long-acting therapy in pregnancy.

Like oral therapy, it is important for patients receiving cabotegravir and rilpivirine to adhere to the schedule of injections to reduce the risk of virological failure. In the ATLAS-2M trial, virological failure was confirmed in two patients having monthly injections and eight patients having injections every eight weeks. Patients who miss scheduled injections by more than a few days will need oral therapy. This is to try and reduce the risk of developing viral resistance.

Although there are problems with injection-site reactions, cabotegravir and rilpivirine offer a new option for people living with HIV. In the FLAIR and ATLAS trials most patients preferred the long-acting injectable drugs to oral therapy.

**REFERENCES**


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.
Cemiplimab

**Approved indications:** Cutaneous squamous cell carcinoma, basal cell carcinoma, non-small cell lung cancer

**Libtayo (Sanofi)**

350 mg concentrate for dilution

Programmed death-ligands 1 and 2 can be expressed by tumour cells or cells within the tumour microenvironment. When these ligands bind with programmed cell death-1 (PD-1), an immune checkpoint, T-cell function is downregulated. By causing dysregulation of T-cell function, tumours can then evade the immune response. Immunotherapy to block the ligands from binding to the PD-1 receptor is therefore an attractive antitumour treatment approach. Cemiplimab is a fully human immunoglobulin G4 monoclonal antibody that binds to the PD-1 receptor. By inhibiting its interaction with the ligands, T-cell responses are stimulated.

Cemiplimab is indicated for two types of skin cancer in Australia. These are cutaneous squamous cell carcinoma in adults who cannot undergo curative surgery or curative radiation, and basal cell carcinoma in adults previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate. Cemiplimab is also indicated for the first-line treatment of certain locally advanced or metastatic non-small cell lung cancers. Its approval for locally advanced disease is only for patients who cannot undergo surgical resection or definitive chemoradiation.

Cemiplimab must be diluted before being given as an intravenous infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity occurs. Steady-state exposure is achieved after approximately four months of treatment. The drug’s elimination is similar to that of other antibodies, with a half-life of 20 days. No dose adjustments are recommended, but data are limited in patients with severe hepatic or renal impairment.

In two open-label phase II trials, patients with cutaneous squamous cell carcinoma were given 3 mg/kg intravenous cemiplimab every two weeks, which has been shown to have similar pharmacokinetics to the dose approved for use in Australia. This regimen induced a complete or partial response in 34 of 78 patients (44%) with locally advanced disease and in 28 of 59 patients (47%) with metastases.

For locally advanced basal cell carcinoma, an open-label phase II trial showed that 26 of 84 patients (31%) achieved a complete or partial response to 350 mg intravenous cemiplimab given every three weeks. The results for patients with metastatic basal cell carcinoma have not yet been reported. In a conference presentation on an interim analysis of the metastatic basal cell carcinoma cohort, cemiplimab was reported to have induced a complete or partial response in six of 28 patients (21%).

Cemiplimab for non-small cell lung cancer was studied in an open-label phase III trial. Patients were randomised to receive 350 mg intravenous cemiplimab given every three weeks or chemotherapy. There was a complete or partial response to cemiplimab in 111 of 283 patients (39%) compared with 57 of 280 patients (20%) who received chemotherapy. The median progression-free survival was 8.2 months with cemiplimab and 5.7 months with chemotherapy. The median overall survival was 14.2 months with chemotherapy, but the median had not been reached with cemiplimab.

As cemiplimab acts on the immune system, it can cause immune-related adverse effects. These include pneumonitis, hepatitis, colitis and endocrinopathies such as hypothyroidism, or more rarely, adrenal or cortical insufficiency. Non-physiological doses of systemic corticosteroids and immunosuppressants should be avoided before starting cemiplimab. However, they can be used after starting treatment to manage immune-mediated adverse reactions. Cemiplimab can also cause severe infusion-related reactions. Doses can be modified and infusions can be discontinued to manage immune-related and infusion-related adverse reactions. Other common adverse events found in clinical trials were fatigue, diarrhoea and hypertension. Cemiplimab is generally well tolerated, with variable rates of discontinuation due to adverse events (7–62%) and low rates of treatment-related death (0–8.2%) found in the trials.

Women should use effective contraception during and for at least four months after treatment. No effects on fertility were observed in animal studies. There are no safety and efficacy data for cemiplimab in children and pregnant women, although animal studies have shown that cemiplimab can cause fetal toxicity. Women should avoid breastfeeding during and for at least four months after treatment.

Cemiplimab appears to have a manageable safety profile in patients with cutaneous squamous cell carcinoma, basal cell carcinoma and non-small cell lung cancer. In Australia, the drug’s approval is only provisional for metastatic and locally advanced cutaneous squamous cell carcinoma and metastatic basal cell carcinoma. The trials for these cancers included small numbers of participants and some doses were different to the recommended dose in Australia. There have been no head-to-head studies.
comparing cemiplimab with other immune checkpoint inhibitors approved for similar indications. Further clinical data are needed to confirm any long-term benefit of cemiplimab.

REFERENCES


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

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https://doi.org/10.18773/austprescr.2022.040
First published 7 July 2022

Elotuzumab

**Approved indication:** multiple myeloma

**Empliciti (Bristol-Myers Squibb)**

vials containing 300 mg or 400 mg powder for reconstitution

Multiple myeloma occurs when cancerous plasma cells accumulate in the bone marrow, outweighing healthy blood cells. The cell surface glycoprotein SLAMF7 has been shown to mediate the adhesion of cancerous plasma cells to the bone marrow in multiple myeloma and to activate natural killer cells, making it an ideal therapeutic target.

Elotuzumab is a humanised (IgG1) monoclonal antibody that targets SLAMF7. It directly enhances natural killer cell activity and antibody-dependent cytotoxicity. Early studies have shown synergistic clinical effects when it is used in combination with immunomodulatory drugs for multiple myeloma.

Elotuzumab is therefore indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in patients who have received at least one therapy previously.

The recommended dose of elotuzumab is 10 mg/kg body weight via slow intravenous infusion on days 1, 8, 15 and 22 for two 28-day cycles and then on days 1 and 15 for subsequent 28-day cycles until disease progression or unacceptable toxicity occurs. Patients must receive premedication with dexamethasone, diphenhydramine or an equivalent H1 blocker, ranitidine or an equivalent H2 blocker, and paracetamol before each dose. Elotuzumab is likely to be metabolised like other monoclonal antibodies, so adverse interactions with other drugs metabolised by the CYP450 system are not expected. It has a serum half-life of about 10 days. On discontinuing elotuzumab, concentrations will decrease to about 3% of the steady-state maximal serum concentration by three months. No dose adjustments are required for renal impairment of any severity or for mild hepatic impairment. Elotuzumab has not been studied in patients with moderate to severe hepatic impairment.

An open-label, randomised, phase III trial (ELOQUENT-2) included adults with multiple myeloma who had received one to three previous therapies and had documented disease progression after their most recent therapy.1 The patients were randomly assigned to receive either elotuzumab plus lenalidomide and dexamethasone, or lenalidomide and dexamethasone alone (control). The median progression-free survival durations were 19.4 months with the elotuzumab regimen and 14.9 months with the control regimen.1 A clinical response was achieved in 79% (252/321) of the patients with the elotuzumab regimen and in 66% (213/325) of the patients with the control regimen.1 Four years after treatment, the median overall survival durations were 48 months with the elotuzumab regimen (rate of 50%) and 40 months with the control regimen (rate of 43%).2

The most common grade 3–4 adverse events in patients receiving elotuzumab in the ELOQUENT-2 trial were lymphocytopenia (77% vs 49% with the control regimen), neutropenia (34% vs 44%), thrombocytopenia (19% vs 20%), anaemia (19% vs 21%) and fatigue (8% vs 8%).1 Infections were reported in 81% of the patients receiving the elotuzumab regimen, compared with 74% receiving the control regimen.1 The incidence of herpes zoster infection was 4.1 per 100 patient-years in those receiving the elotuzumab regimen (vs 2.2 with the control regimen).1 Clinicians should continue to assess patients for the need for antiviral prophylaxis to manage infections. Infusion reactions, such as pyrexia, chills and hypertension, were reported in 10% of those receiving the elotuzumab regimen, with 70% of these reactions occurring with the first dose.1 Treatment may be stopped or the infusion rate may be reduced to manage infusion reactions. Two patients (1%) discontinued treatment because of infusion reactions that did not resolve, and 2% of patients receiving either regimen died due to infections or other disorders.1 At the four-year follow-up, the adverse events were similar to those observed in the first part of the ELOQUENT-2 trial.2

As with all therapeutic proteins, there is a potential for immunogenicity with elotuzumab. Of 299 patients receiving the elotuzumab regimen who were tested for the presence of neutralising antibodies, 45 (15%) tested positive at least once.1 There are no data on the drug’s effects on fertility. The safety and efficacy of elotuzumab have not been studied in children or pregnant women. As the drug is taken in combination with lenalidomide, women should avoid pregnancy during treatment, during dose interruptions and for four weeks after stopping treatment.

Clinical trial data suggest that the addition of elotuzumab to a regimen of lenalidomide and dexamethasone improves progression-free survival in patients with relapsed or refractory multiple myeloma who have received previous therapies. In a study including newly diagnosed, previously untreated patients, no significant clinical benefits were observed on adding elotuzumab to lenalidomide and dexamethasone.3 Elotuzumab has also been studied with other drug combination regimens, such as pomalidomide and bortezomib.4,5 In previously...
treated patients, the addition of elotuzumab to immunomodulatory drugs results in improved clinical benefit with an increase in adverse events, which should be managed accordingly. The benefits of elotuzumab plus lenalidomide and dexamethasone appear favourable for four years in patients with multiple myeloma.

manufacturer provided relevant information

REFERENCES


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.
Onasemnogene abeparvovec

**Approved indication: spinal muscular atrophy**

Zolgensma (Novartis)

**vials containing 2x10^{12} vector genomes/mL**

Spinal muscular atrophy is an autosomal recessive genetic disorder. Mutations in the survival motor neuron (SMN) 1 gene lead to a deficiency of SMN protein. This results in the loss of motor neurons and therefore reduced muscle function. The severity of the disease depends on how much SMN protein can be produced by another gene (SMN2). In the most severe form of the disease, spinal muscular atrophy type 1 (SMA1), the infant is unable to sit upright and usually requires ventilation before the age of two years.

As there is no effective treatment for spinal muscular atrophy there has been research into gene therapy to correct the underlying disorder. Infusing a copy of the gene could increase concentrations of SMN protein. A phase I trial tried gene therapy in 15 infants with SMA1. Following a single infusion of genetic material at 3–6 months of age, the infants’ motor function improved. They were all still alive at 20 months of age and did not require permanent mechanical ventilation.

**Onasemnogene abeparvovec** is a genetically engineered copy of the human SMN gene delivered by an adeno-associated viral vector. The dose is determined by the weight of the child and is given by intravenous infusion over one hour. The vector spreads through the body and is shed in saliva, urine and the faeces. Most of it is cleared within one month and the virus is not expected to cause infections.

An open-label phase III trial in the USA enrolled 22 babies (mean age 3.7 months) with SMA1. They had bi-allelic mutations of the SMN1 gene with one or two copies of the SMN2 gene. After a single infusion of onasemnogene abeparvovec, they were followed up until they were 18 months old. By this age, 59% (13/22) were able to sit at least 10 seconds and 82% (18/22) did not require ventilation. One infant died during the trial.

A similar trial in Europe treated 33 patients (mean age 4.1 months). By 18 months 44% (14/32) had been able to sit for at least 10 seconds and 97% (31/32) did not require ventilation. One infant died.

Another open-label trial investigated giving onasemnogene abeparvovec to babies who were expected to develop spinal muscular atrophy. These presymptomatic babies had bi-allelic mutations with two or three copies of SMN2. They were treated before they were six weeks old. All of the 14 children with two copies of SMN2 were able to sit independently for at least 30 seconds by the age of 18 months. The 15 children with three copies of SMN2 were all able to stand for at least three seconds at the age of two years and 14 were able to walk.

Adverse reactions to onasemnogene abeparvovec are common. A review of safety data from several trials identified hepatotoxicity, thrombocytopenia, and cardiac adverse events as potential problems. Liver function tests, platelet counts and troponin concentrations therefore require monitoring. To reduce the effect on liver function, prednisolone is recommended for 30 days, starting before the infusion. Patients are also at risk of immune reactions and thrombotic microangiopathy. Approximately half of the patients will develop a fever after treatment.

While the quantity of long-term data is limited by the rarity of the disease, the children from the phase I trial have now been followed up for five years. The 10 who received the therapeutic dose of onasemnogene abeparvovec all survived and did not require permanent ventilation.

Although the outcomes for children given onasemnogene abeparvovec appear better than the historical outcomes in SMA1, there is still substantial motor impairment. Patients who have already had irreversible damage to their motor neurons may be less likely to benefit from therapy. Experience in Australia with onasemnogene abeparvovec supports early treatment. The Australian indication includes presymptomatic cases and the approval is restricted to infants under nine months old.

REFERENCES


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.
Risdiplam

Approved indication: spinal muscular atrophy
Evrysdi (Roche)
bottles containing 60 mg in 2 g powder for reconstitution as 0.75 mg/mL oral solution

The most common form of spinal muscular atrophy is due to mutations in a gene located on chromosome 5. This is sometimes referred to as 5q SMA. As a result of the mutation there is reduced production of survival motor neuron (SMN) protein. This leads to progressive muscle weakness. The most frequent type of spinal muscular atrophy (SMA1) presents in babies as hypotonia, poor head control and impaired swallowing. Due to neuromuscular weakness, respiratory support will be needed and life expectancy is usually under two years.

A related gene (SMN2) can produce some SMN protein. However, the molecule is truncated so research has investigated how to produce more functional protein. One option is to use nusinersen, an antisense oligonucleotide which enables SMN2 to produce full-length SMN protein. Another option is risdiplam, a modifier of pre-mRNA splicing which also enables production of full-length protein.

The dose of risdiplam is determined by the age and weight of the child. The oral solution is given once daily. It cannot be mixed with milk and formula and should be given after feeding. Risdiplam can cross the blood–brain barrier. It is metabolised by several enzymes including cytochrome P450 (CYP) 3A4, however no dose adjustments are needed with inhibitors of CYP3A, such as itraconazole. Most of the dose is excreted as metabolites mainly in the faeces. The half-life is approximately 50 hours. There have been no studies of risdiplam in patients with renal or severe hepatic impairment.

The open-label FIREFISH trial is studying risdiplam for the management of 5q-autosomal recessive spinal muscular atrophy in patients with two copies of SMN2. The first part of the trial established that the daily dose for infants should be 0.2 mg/kg. After four weeks this dose had doubled the baseline concentration of SMN protein.

In the second part of the trial 41 infants (median age 5.3 months) were assessed after taking risdiplam for 12 months. By then 29% (12/41) of the infants were able to sit unsupported for at least five seconds. Approximately 85% (35/41) were still alive and did not require permanent ventilation. Three infants died from respiratory complications.

The SUNFISH trial also studied 5q SMA but was double-blind and enrolled older patients (median age 9 years). Based on the first part of the trial, the dose of risdiplam for patients weighing at least 20 kg was 5 mg daily. Risdiplam was given to 120 people while 60 were given a placebo. Efficacy was assessed using the Motor Function Measure (range 0–96). After 12 months this score had increased by 1.36 points from an average of 45.48 in the patients taking risdiplam. In the placebo group the score declined by 0.19 points from a baseline of 47.35. The largest improvement was in younger patients with no improvement in the 18–25 years age group. No patients died.

The effect of risdiplam on pre-mRNA splicing is not confined to the gene coding for SMN protein. Its effect on other genes may explain some of its adverse effects. Risdiplam was embryo-fetotoxic in animal studies and may reduce male fertility. In the SUNFISH trial adverse effects that were more frequent with risdiplam than with placebo included fever, pneumonia, urinary tract infection, diarrhoea, rash and mouth ulcers.

Risdiplam may improve the survival of infants compared to historical controls, but its overall effectiveness is not clear. In the SUNFISH trial there was little difference from placebo for some outcomes. While the difference in the primary end point was statistically significant, it is difficult to interpret the clinical significance of a 1.55 difference on a 96-point scale. In the SUNFISH trial the clinicians thought 48% of the patients given risdiplam had improved, but so had 40% of the placebo group. Although the approved indication is for the treatment of 5q SMA, risdiplam may not be effective for some types of the disease. As younger patients seem to have the better outcomes, early intervention may have the best chance of a meaningful response. Risdiplam can be used in infants from the age of two months, but its role in pre-symptomatic children is still under investigation. It also remains to be seen if any of the adverse effects, such as retinal toxicity reported in animal studies, appear during long-term therapy. While risdiplam will be easier to administer than nusinersen, which requires lumbar puncture, the role of both drugs will need to be considered in the context of emerging gene therapy for spinal muscular atrophy.

REFERENCES


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.
Sacituzumab govitecan

**Approved indication:** breast cancer

**Trodelvy (Gilead Sciences)**

**Vials containing 180 mg powder for reconstitution with 0.9% sodium chloride**

Breast cancer typically expresses one or more of three key receptors, which are the oestrogen, progesterone and HER2 receptors. Triple-negative breast cancer is a type of breast cancer that does not express any of these receptors, so it is not responsive to hormonal drugs or drugs that target HER2. Patients with previously treated metastatic triple-negative breast cancer have a poor prognosis as standard chemotherapy has a low response rate and progression-free survival is short. In most cases of triple-negative breast cancer, trophoblastic antigen-2 (Trop-2) is highly expressed and is therefore a feasible therapeutic target.

Sacituzumab govitecan consists of an antibody against Trop-2 conjugated with SN-38, the active metabolite of the topoisomerase inhibitor irinotecan. Sacituzumab govitecan binds to the cancer cells, and the release of SN-38 within the cells leads to apoptosis.

The recommended dose is 10 mg/kg via slow intravenous infusion once per week on days 1 and 8 of continuous 21-day treatment cycles until disease progression or unacceptable toxicity. There have been no studies of the metabolism of sacituzumab govitecan, but SN-38 is metabolised by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). The activity of this enzyme may be reduced by certain genetic variants of the UGT1A1 gene. These variants may put some patients at an increased risk of adverse reactions such as neutropenia and anaemia. Co-treatment with UGT1A1 inhibitors, such as propofol, ketoconazole and EGFR tyrosine kinase inhibitors, may increase the risk of adverse reactions due to an increase in exposure to SN-38. Co-treatment with UGT1A1 inducers, such as carbamazepine, phenytoin, rifampicin, ritonavir and tipranavir, should also be avoided due to a substantial reduction in exposure to SN-38. However, no drug–drug interaction studies have been conducted. The efficacy and safety of sacituzumab govitecan in patients with moderate to severe renal or hepatic impairment are currently unknown.

Sacituzumab govitecan was compared to chemotherapy with eribulin, vinorelbine, capecitabine or gemcitabine in the ASCENT study.¹ This multicentre, open-label phase III trial randomised patients with metastatic triple-negative breast cancer who had previously received a taxane and at least two chemotherapies. All the patients in the trial received treatment until disease progression or unacceptable toxicity occurred. Although the trial included some patients with brain metastases, they were excluded from the primary analysis to minimise the confounding effects of this factor for poor prognosis. After a median follow-up of 17.7 months, a complete or partial clinical response was achieved in 35% (82/235) of the patients receiving sacituzumab govitecan and in 5% (11/233) of the patients receiving chemotherapy. The median duration of response was longer with sacituzumab govitecan than with chemotherapy (6.3 months vs 3.6 months). The median time to response was 1.5 months in both treatment arms. The median duration of progression-free survival was 5.6 months with sacituzumab govitecan and 1.7 months with chemotherapy. The median overall survival was 12.1 months with sacituzumab govitecan and 6.7 months with chemotherapy.¹

In the ASCENT study, haematological treatment-related events of grade 3 or higher severity included neutropenia (51% with sacituzumab govitecan vs 33% with chemotherapy), leukopenia (10% vs 5%), anaemia (8% vs 5%) and febrile neutropenia (6% vs 2%). Severe gastrointestinal treatment-related events included diarrhoea (10% with sacituzumab govitecan vs <1% with chemotherapy), with lower incidences of nausea, vomiting and abdominal pain that were more frequent with sacituzumab govitecan than with chemotherapy. Fatigue and asthenia of all grades were also frequent with sacituzumab govitecan, and caution is advised when driving or operating machines. Adverse events led to 5% of the patients in each arm of the ASCENT study discontinuing treatment. There were three deaths owing to adverse events in each arm.¹

Sacituzumab govitecan can cause hypersensitivity reactions, including anaphylaxis. To prevent infusion reactions, antihistamines and H1 and H2 antagonists should be given before each dose, and corticosteroids may be given to patients with a history of infusion reactions. In addition, to prevent chemotherapy-induced nausea and vomiting, a two- or three-drug antiemetic combination regimen should be given before each dose. Doses of sacituzumab govitecan are reduced or discontinued to manage adverse reactions. The dose should not be re-escalated after it has been reduced.

Based on animal studies, sacituzumab govitecan may impair fertility in women of reproductive potential. It can cause teratogenicity and embryo-fetal lethality. Women should be advised of the potential risk to a fetus and should use contraception during treatment and for six months after the last dose. Male patients with female partners should use contraception during treatment and for three months after the last dose.
In terms of clinical benefit, the ASCENT trial favoured sacituzumab govitecan over chemotherapy in patients with metastatic triple-negative breast cancer previously treated for unresectable locally advanced or metastatic disease. However, the treatment has several well-defined toxic effects that require early recognition and management. Further studies of sacituzumab govitecan as a component of different combination and neoadjuvant regimens for breast cancer are ongoing.


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.
Trastuzumab deruxtecan

Approved indication: breast cancer

Enhertu (Astra Zeneca) vials containing 100 mg powder for reconstitution

Since it first became available over 20 years ago, the monoclonal antibody trastuzumab has become a standard part of the management of HER2-positive breast cancer. For patients with metastatic cancer that has progressed despite treatment, trastuzumab has been combined with a cytotoxin. Although this combination, trastuzumab emtansine, can improve progression-free survival, the cancer is likely to progress again. There is then uncertainty about the best option for third-line therapy.

A possible option is trastuzumab deruxtecan. In this product the anti-HER antibody is conjugated with deruxtecan, a topoisomerase inhibitor. This conjugate is reconstituted with sterile water then diluted with 5% dextrose and given as a slow intravenous infusion. It is incompatible with sodium chloride solution. The conjugate is stable in plasma, but after binding to HER2 it is cleaved by lysosomal enzymes within the cancer cells. Release of cytotoxic deruxtecan causes apoptosis. The drug:antibody ratio of trastuzumab deruxtecan is greater than that of trastuzumab emtansine. While trastuzumab is cleared like other antibodies, deruxtecan is metabolised by cytochrome P450 (CYP) 3A4 but no dose adjustment is recommended for patients taking inhibitors of CYP3A. Most of the deruxtecan is thought to be excreted in the faeces. Blood counts were reduced, effects were nausea, fatigue, alopecia, vomiting and constipation. Blood counts were reduced, approximately 35% of the patients having a decreased neutrophil count. There is a risk of febrile neutropenia and neutropenia is one reason for interrupting treatment. Another reason is a reduction in left ventricular ejection fraction. During the phase II trial 13.6% of the women developed interstitial lung disease, including some fatal cases. While asymptomatic cases may respond to an interruption of therapy, symptomatic interstitial lung disease is an indication for stopping trastuzumab deruxtecan. As the conjugate has cytotoxic effects, pregnancy should be avoided. Reflecting the results of the phase II trial, trastuzumab deruxtecan has been provisionally approved for use in patients with unresectable or metastatic HER2-positive breast cancer that has already been treated with two or more anti-HER2 regimens. As evidence is limited, its benefits need to be confirmed in a phase III trial.

REFERENCES


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.
Correction

Hormonal contraception and mood disorders [Correction]
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First published 23 June 2022

The article on hormonal contraception and mood disorders (Aust Prescr 2022;45:75-9) has been corrected. View corrected article.

In Table 1, which lists progestogen-only hormonal contraceptives, ‘Medroxyprogesterone acetate, oral 2.5, 5, 10 mg Provera’ should be removed, and replaced with ‘Drospirenone 4 mg Slinda’.

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