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# Opioid prescribing in dentistry – is there a problem?

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drug misuse, non-steroidal  
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opioids, paracetamol

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In light of Australia's opioid crisis, it is important to recognise the role of dental prescribing in the context of this serious public health issue.

There is little role for opioids in dentistry given that there are established superior analgesics. Identifying and addressing the cause of pain by active dental treatment is the best pain management – analgesia plays an adjunctive role only.

In a survey, 16–27% of dentists preferred prescribing an opioid or paracetamol over a non-steroidal anti-inflammatory drug (NSAID) as first choice for dental pain.<sup>1</sup> The most commonly prescribed opioids in dentistry are codeine 30 mg (with paracetamol 500 mg), oxycodone and tramadol. Paracetamol combined with codeine accounts for around 96% of these prescriptions.<sup>2</sup> This is of concern since in 2016 codeine products (both over-the-counter and prescription) were the most commonly misused pharmaceutical products, followed by oxycodone and tramadol.<sup>3</sup>

Numerous studies have found that NSAIDs are superior to opioids for dental pain. They attenuate the inflammatory process, which occurs after procedures such as a tooth extraction, while opioids only block the perception of pain. Randomised controlled trials have also shown that codeine does not provide additional pain relief when combined with standard doses of ibuprofen and paracetamol after surgical wisdom teeth removal.<sup>4</sup> Various dose combinations of paracetamol with ibuprofen provided superior pain relief compared with paracetamol and codeine combinations after impacted third molar extractions.<sup>5</sup>

When presented with patients experiencing dental pain, education should focus on the importance of local dental treatment and the recommended analgesics NSAIDs and paracetamol. If opioids need to be prescribed, the lowest dose for the shortest duration of oxycodone should be used (maximum of 3 days) as recommended by Therapeutic Guidelines, Oral and Dental.<sup>6</sup> Patients should also be warned about the adverse effects, tolerance and dependence potential of opioids.

Codeine is no longer recommended by the Therapeutic Guidelines.<sup>6</sup> It was rescheduled to a prescription-only medicine in February 2018.<sup>7</sup> Since then, codeine misuse and sales appear to have reduced overall.<sup>8</sup> However, there was an increase in dental prescriptions of codeine 30 mg (with paracetamol 500 mg) and oxycodone by 21% and

24% respectively one year after the rescheduling in comparison to the previous year.<sup>9</sup>

There is evidence that people can become dependent on opioids as a result of codeine initiated for dental pain.<sup>10</sup> In the United States a pre-filled opioid prescription, given for the extraction of wisdom teeth, has been found to be an independent risk factor for persistent opioid use.<sup>11</sup>

Dentists may also be targets of 'doctor shopping', in which drug-dependent people seek drugs for misuse from multiple prescribers.<sup>12</sup> Including dentists in real-time prescription monitoring programs would allow them to make more informed prescribing decisions. These monitoring systems can currently only be accessed by pharmacists, doctors and nurses.

As it is established that the most common source of drugs for misuse is leftover pills from legitimate prescriptions, it is of concern that dentists are able to prescribe standard Pharmaceutical Benefit Schedule pack sizes when often fewer tablets would be sufficient. In light of this, the Pharmaceutical Benefits Advisory Committee has recently recommended that some immediate-release opioid pack sizes be reduced with increased restricted listings and smaller maximum quantities.<sup>13</sup>

The early identification of people at higher risk of developing drug dependence would assist prescribers in clinical practice. Characteristics of opioid-dependent individuals include pre-existing chronic pain, mental health conditions and a history of any substance misuse.<sup>10</sup> If a dentist suspects a patient is seeking opioids for non-medical use, they should avoid prescribing opioids and focus on providing active dental treatment and recommend NSAIDs and paracetamol (if appropriate and when indicated).

Given the established misuse of pharmaceutical opioids, their limited efficacy in dental pain and their potential for misuse, opioids should only be prescribed for dental pain if NSAIDs and paracetamol have not been effective or cannot be tolerated. Clinicians should ensure that a therapeutic need exists, prescribe minimal quantities to avoid leftover pills and be aware of people intentionally seeking to acquire drugs for misuse. Also, education about the abuse potential of opioids should include dentists to reduce unnecessary prescribing when superior options exist. ◀

*Conflict of interest: none declared*

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# Management of autoimmune disease during the COVID-19 pandemic

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Immunosuppression is an important part of the management of autoimmune diseases. As with all treatments, immunosuppressants are prescribed based on a balance of harm and benefit. This balance needs to be re-evaluated in the context of the pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). However, as the pandemic is rapidly evolving, this evaluation must be made with constantly changing, imperfect information. The evaluation must also consider each person's risk of exposure and infection, public health measures and a range of risk factors.

When coronavirus disease (COVID-19) emerged, there was concern regarding the potential for poor outcomes in patients taking immunosuppressive drugs for rheumatic diseases. As the pandemic has evolved, reports have added to our understanding of the outcomes for patients who are already taking immunosuppressant drugs. However, these studies have limitations which need to be considered when making recommendations based on this information.

In discussions about COVID-19 with patients taking immunosuppressants, the first consideration is their risk of being infected. This depends on local epidemiological factors such as the numbers of active cases and the level of community transmission. For example, the risk of infection will be much higher for a patient living in a community with high levels of transmission compared to a patient working exclusively at home in an area with a low prevalence. These risks will vary throughout the pandemic, influenced by public health measures such as case finding and isolation, physical distancing and hand hygiene.

If a patient is infected, the risk of an adverse outcome depends on modifiable and non-modifiable factors. Non-modifiable risk factors include older age and comorbidities. Initial data from 600 patients with rheumatic diseases who were infected do not show any difference in the risk of hospitalisation for COVID-19 between patients with rheumatoid arthritis, and patients with systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis or vasculitis.<sup>1</sup> Another series of 86 patients from New York found no increase in hospitalisation for patients with rheumatic disease compared to the background rate in the community. The mortality rate was 1%, which was consistent with general cohorts of COVID-19 patients.<sup>2</sup>

Modifiable risk factors for adverse outcomes in COVID-19 include drugs. So far there has not been any increase in the risk of hospitalisation for COVID-19 in rheumatic disease patients taking disease-modifying antirheumatic drugs alone (e.g. methotrexate) or in combination with biologics or Janus kinase inhibitors, compared to patients who were not taking these drugs.<sup>1</sup> Similarly, non-steroidal anti-inflammatory drugs and hydroxychloroquine did not alter the risk of hospitalisation with COVID-19. Treatment with tumour necrosis factor inhibitors reduced the odds of hospitalisation, with an adjusted odds ratio (aOR) of 0.4 (95% confidence interval (CI) 0.19–0.81). However, prednisone at a dose of 10 mg or more increased the odds of hospitalisation – aOR 2.05 (95% CI 1.06–3.96).<sup>1</sup> Another study of people infected with COVID-19 compared 52 patients with rheumatic disease, including 39 taking immunosuppressants, with 104 matched COVID-19 positive controls. There was no significant difference between the groups in hospitalisation, length of stay in hospital, oxygen therapy or death. However, patients with rheumatic disease were more likely to require intensive care or ventilation.<sup>3</sup>

In a series of 525 patients with inflammatory bowel disease, poorer outcomes with COVID-19 were associated with increasing age, comorbidities and systemic glucocorticoids. Tumour necrosis factor inhibitors were not associated with an increased risk of a poor outcome. Aminosalicylates, such as sulfasalazine, were associated with some composite end points of poor outcome but not others, so caution is required when interpreting this result and further study is required.<sup>4</sup>

When advising patients taking immunosuppressive drugs during the pandemic, a comprehensive risk assessment should consider the consequences of changing treatment. Stopping the drugs could cause a flare of the underlying disease or other disease complications.

As with all treatment decisions, patients have their own values and tolerances for risk. Patients are often substantially influenced by personal, financial and social factors. General guidance is often helpful, with subsequent adjustments to suit the patient's own situation. The American College of Rheumatology (ACR) and the European League Against Rheumatism recommend that in the absence

of confirmed or suspected COVID-19, treatment for rheumatic disease should not be altered.<sup>5,6</sup> If SARS-CoV-2 infection is confirmed, ACR guidelines suggest suspending immunosuppression, however they do state that as part of a shared decision-making process interleukin-6 inhibitors may be continued. The potential to continue therapy may be extended to other immunosuppressants in later versions of the guidelines.

As we learn more about immunosuppressed patients and their response to COVID-19 our approach will undoubtedly be refined. For now, we need to recognise that there is no right answer – the limited information we have must be tailored to each patient. ◀

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*Evan Bursle has received speaker fees from Gilead, Novartis and Pfizer.*

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# Migraine management

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calcitonin gene-related  
peptide, migraine, triptans

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**SUMMARY**

Migraine causes significant lost time from everyday activities. Addressing lifestyle triggers and comorbidities in patients with migraine is the first step of management.

Acute migraine treatments primarily manage the headache component and should be started as early as possible in the migraine attack.

Prophylaxis may be recommended if a patient is having three or more migraines a month or if their migraines are difficult to manage.

The choice of prophylactic drugs should be tailored to the individual's potential for adverse effects, interactions and comorbidities.

**Introduction**

Migraine is more than just a headache – it has associated features including sensitivity to light or noise, nausea and avoidance of exertion. The headache is typically throbbing and severe. As such, migraine is debilitating and is the leading cause of disability in people under 50 years old.<sup>1</sup>

**Pathophysiology**

Migraine is a common, polygenetic brain disorder with complex biology. The vascular reactivity of aura is now considered to be a secondary symptom that occurs alongside migraine. There is convergence of peripheral trigeminal sensory nerves on the single pain centre of the trigeminocervical complex. The central mechanisms include neurotransmitter pathways such as serotonin, calcitonin gene-related peptide and other neuropeptides.<sup>2</sup>

**Assessing the patient**

To distinguish migraine from other causes of headache, ask the patient about the character and location of the headache as well as associated features and avoidance of exertion. Differentiating between episodic and chronic migraine is an arbitrary but useful cut off for some treatment options (see Fig.). In clinical practice, patients highlight their worst migraines. To ascertain the true frequency of headaches, enquire about the number of completely headache-free days per week or month.

**Management approach**

Addressing lifestyle triggers and comorbidities in patients with migraine can be particularly beneficial for patients. Sleep disorders, dietary triggers (e.g. some types of alcohol, cheese, oranges and chocolate), dehydration and caffeine overuse are important to recognise and manage. Healthy body

weight and exercise are recommended. Depending on the individual triggers, behavioural and psychological strategies and physical therapy can help some patients. Commonly used natural migraine preventives include magnesium, riboflavin, coenzyme Q-10, and Feverfew. These have limited and variable levels of evidence for efficacy and are not the mainstay of treatment.<sup>3,4</sup>

**Pharmacotherapy**

Drugs can be used to treat acute migraine, or they can be used prophylactically to reduce the frequency and severity of attacks. The Therapeutic Guidelines has recently updated its guidance on headache, including general principles, specific dosing recommendations, and advice for children and pregnant women.<sup>5</sup>

**Treating acute migraine**

Treatments for acute migraine aim to abort the headache stage of migraine within 1–2 hours. Although effective for this, they do not significantly help with the prodromal, aura or postdromal stages. Treatment should be started as early as possible in the headache phase and some patients will require a combination of therapies. Common medicines used include paracetamol, aspirin (900–1000 mg per dose) or other non-steroidal anti-inflammatory drugs (NSAIDs), antiemetics and triptans.<sup>6,7</sup>

**Triptans**

As they are more selective against migraine, triptans (5HT<sub>1</sub> agonists) may be first-line drugs for patients with moderate–severe pain, or when simple analgesics have not been effective. Triptans cause vasoconstriction and are not recommended in patients with cardiovascular disease.<sup>8</sup> There are five triptans available in Australia. Guidelines recommend trying triptans sequentially to find the

best tolerated and most effective option for the individual. Eletriptan, rizatriptan and zolmitriptan have the highest pain-free rates at two hours and naratriptan is associated with lower adverse effects (see Table).<sup>2,9,10</sup>

Depression and anxiety are common comorbidities with migraine. The risk of serotonin syndrome when triptans are used in conjunction with selective serotonin reuptake inhibitors or serotonin and noradrenaline reuptake inhibitors is low. A recent retrospective data analysis showed there were only two confirmed cases of serotonergic syndrome in a cohort of 19,017 patients who were co-prescribed a triptan and an antidepressant.<sup>11</sup>

Medicine overuse can worsen migraine. Triptans should therefore be limited to less than 10 days a month and simple analgesics to no more than 15 days a month. Opioids are not recommended for migraine due to limited effectiveness and the risk of drug overuse.

### Managing nausea

Intercurrent nausea can impair absorption so taking an antiemetic with the first analgesic can help.<sup>12</sup> If patients are unable to take oral medicines, other routes of administration can be considered:

- non-oral triptan formulations
- suppositories, such as NSAIDs (indometacin or diclofenac)
- ondansetron wafers for nausea and vomiting
- prochlorperazine suppositories.

Fig. Principles of migraine management

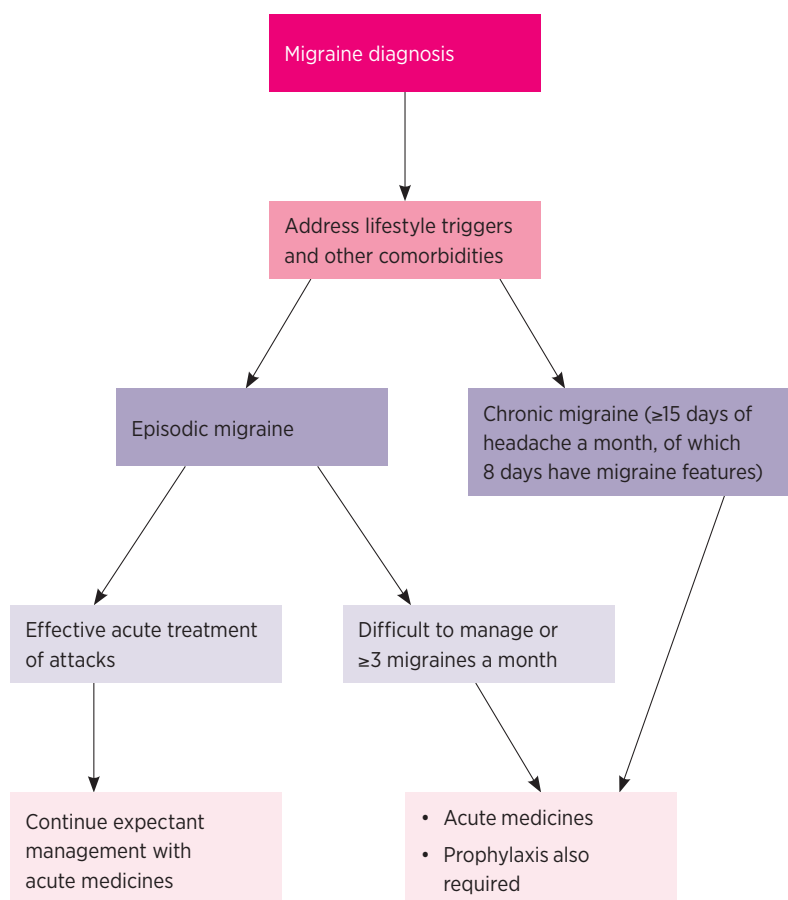


Table Triptans available in Australia for migraine<sup>2,9,10</sup>

Generic name	Formulation	Dosing (maximum dose)	Initial 2-hour relief	Sustained pain free	Tolerability
Sumatriptan	Tablet or fast disintegrating tablet	50–100 mg (300 mg/day)	=	=	=
	Nasal spray (10 mg or 20 mg)	10–20 mg one nostril (40 mg/day)			
	Subcutaneous injection*	6 mg autoinjector (12 mg/day)			
Rizatriptan	Tablet or wafer	10 mg (30 mg/day)	+	+	=
Eletriptan	Tablet 40 mg	40–80 mg (160 mg/day)	=/+	=/+	=
	Tablet 80 mg		+	+	–
Zolmitriptan	Tablet	2.5–5 mg (10 mg/day)	=	=	=
Naratriptan	Tablet	2.5 mg (5 mg/day)	–	–	++

\* sumatriptan injection not subsidised on Pharmaceutical Benefits Scheme

Using 100 mg sumatriptan as the comparator:

= indicates no difference

+ indicates better

– indicates inferior, when compared with sumatriptan

## ARTICLE

## Migraine management

**Menstrual migraines**

Menstrually related migraine attacks are more severe, more difficult to treat and more likely to recur. A combined oral contraceptive pill can be used for up to six consecutive months to limit the number and choose the timing of the menstrually related attacks. However, the combined oral contraceptive pill should be avoided in migraine with aura due to the risk of stroke. In addition, some patients have increased migraine attacks on a combined contraceptive pill. Non-steroidal anti-inflammatories (such as naproxen) may help if there are any perimenstrual symptoms, in addition to the usual acute therapies.<sup>13</sup>

**Box Preventive treatments for migraine****As first-line drugs in adults, use:**

- amitriptyline\* 10 mg orally, once daily at night. Increase daily dose by 10 mg at intervals of at least 1 week (maximum daily dose 75 mg). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy

OR

- candesartan\* 4 mg orally, once daily. Increase daily dose by 4 mg at intervals of at least 1 week (maximum daily dose 32 mg). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy

OR

- nortriptyline\* 10 mg orally, once daily at night. Increase daily dose by 10 mg at intervals of at least 1 week (maximum daily dose 75 mg). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy

OR

- pizotifen 0.5 mg orally, once daily at night. Increase daily dose by 0.5 mg at intervals of at least 1 week (maximum daily dose 1.5 to 3 mg). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy

OR

- propranolol 20 mg orally, once daily at night. Increase daily dose by 20 mg at intervals of at least 1 week (maximum daily dose 160 mg in 2 or 3 divided doses). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy

OR

- sodium valproate\*\* 200 mg orally, once daily at night. Increase daily dose by 200 mg at intervals of at least 1 week (maximum dose 500 mg twice daily). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy

OR

- topiramate 25 mg orally, once daily at night. Increase daily dose by 25 mg at intervals of at least 1 week (maximum dose 100 mg twice daily). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy

OR

- verapamil\* sustained-release 90 mg orally, once daily. Increase daily dose slowly over 3 weeks (maximum daily dose 240 mg). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy.

\* At the time of writing, this drug is not approved by the Australian Therapeutic Goods Administration (TGA) for migraine prophylaxis. See the TGA website for current information [www.tga.gov.au](http://www.tga.gov.au).

† Avoid sodium valproate in females of childbearing potential (see eTG complete [www.tg.org.au](http://www.tg.org.au) for information on teratogenic and neurodevelopmental effects of antiepileptic drugs).

See eTG complete for more detailed information on migraine prophylaxis [www.tg.org.au](http://www.tg.org.au). Reproduced with permission from Migraine [Published 2017 Nov. Amended 2019 Jan]. In: eTG complete [digital]. Melbourne: Therapeutic Guidelines Limited; 2019 Dec. [www.tg.org.au](http://www.tg.org.au)<sup>5</sup>

**Migraine prophylaxis**

Prophylactic therapy<sup>14,15</sup> is generally indicated in patients with:

- three or more severe headache days per month causing functional impairment that are not consistently responsive to acute treatments
- more than 6–8 headache days per month despite responsiveness to acute treatments
- contraindications to acute migraine treatments
- particularly disabling symptoms even if infrequent attacks (such as brainstem aura, hemiplegic migraine, syncope)
- ongoing significant impact to a patient's functioning despite lifestyle modifications, trigger management and use of acute treatments
- risk of drug overuse headache.

Considerations for choice of preventive medicines include evidence for efficacy, adverse effect profile, drug interactions, contraindications, patient comorbidities, costs, availability and patient preference.

All oral prophylactic drugs for migraine were developed for other purposes such as hypertension, depression and epilepsy. In general, they alter the neurotransmitters involved in migraine. Their efficacy can only be fully assessed after 8–12 weeks at a therapeutic dose.

Antihypertensives used for prophylaxis include calcium channel blockers (such as verapamil), beta blockers (such as propranolol), and angiotensin II receptor inhibitors (such as candesartan). Antidepressants include amitriptyline and nortriptyline. Antiepileptic drugs are also used – topiramate is the most evidence-based of the oral migraine preventors, but carries potential adverse effects such as altered mood, verbal fluency issues (word finding) and paraesthesia. Sodium valproate is also prescribed as prophylaxis for migraines (see Box).<sup>5</sup>

Adverse effects and a patient's comorbidities often influence the choice of drug. For instance, medicines with a high risk of weight gain (e.g. pizotifen or sodium valproate) should be avoided in obese patients and beta blockers should be avoided in those with asthma. Antihypertensive drugs should not be given to people with hypotension. Choosing a sedative option at night (e.g. amitriptyline or pizotifen) may be suitable for someone with insomnia.

Drugs such as propranolol and verapamil should not be prescribed for patients with a history of self-poisoning. Similarly, topiramate should be avoided in patients with a history of suicidal ideation.



## Botulinum toxin A

In Australia, if a patient has chronic migraine but has failed to improve with three oral prophylactic medicines or could not tolerate them, they qualify for Pharmaceutical Benefit Scheme (PBS) subsidised onabotulinum toxin A (Botox) therapy. This is given by a neurologist. Contrary to popular belief, this treatment does not work by relaxing the scalp, face or neck muscles (although the latter can be of additional benefit in some patients), but rather it slowly improves the migraine frequency and severity by altering the neurotransmitters involved in migraine. This treatment requires 31 injections subcutaneously in the head and neck every three months. Overall this is well tolerated without drug interactions or systemic adverse effects. However, headache, neck weakness, redness at the injection sites and heaviness of the eyelids are possible adverse effects.<sup>16</sup>

## Monoclonal antibodies

A new class of injectable prophylactic drugs targeting calcitonin gene-related peptide (CGRP) have emerged recently. These appear to be well tolerated and reduce migraine frequency. Erenumab is a CGRP-receptor antibody, while fremanezumab and galcanezumab target the CGRP ligand. They are given as monthly subcutaneous injections.<sup>17</sup> At the time of writing, there is approval for erenumab,

fremanezumab and galcanezumab by the Therapeutic Goods Administration but not listed for PBS use yet in Australia, so access to this class of drug remains limited due to cost.

## Conclusion

Migraine management starts with a correct diagnosis. Treatment of acute attacks requires early and effective medicines. If simple analgesics are inadequate, triptan drugs may be more effective.

Preventive strategies to reduce migraine attacks include lifestyle modifications, management of comorbidities, behavioural and physical therapies, and pharmacological treatments. The choice of prophylactic medicines is guided by potential interactions, adverse effects and patient comorbidities. Novel preventive therapies such as the anti-CGRP monoclonal antibodies are targeted therapies to consider.

Managing migraine with acute and preventive strategies for those significantly affected can reduce the disability and loss of function caused by this disease. ◀

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## ARTICLE

# Prescribing medicinal cannabis

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**SUMMARY**

The Australian Federal Government legalised access to medicinal cannabis in 2016.

More than 100 different cannabis products are now available to prescribe. Most are oral preparations (oils) or capsules containing delta-9-tetrahydrocannabinol or cannabidiol. Dried-flower products are also available.

As most products are unregistered drugs, prescribing requires approval under the Therapeutic Goods Administration Special Access Scheme-B or Authorised Prescriber Scheme.

Special Access Scheme Category B applications can be made online, with approval usually being given within 24–48 hours. However, supply chain problems may delay dispensing by the pharmacy.

By the end of 2019, over 28,000 prescribing approvals had been issued to patients, involving more than 1400 doctors, mostly GPs. More than 70,000 approvals are projected by the end of 2020.

Most prescriptions are for chronic non-cancer pain, anxiety, cancer-related symptoms, epilepsy and other neurological disorders. However, the evidence supporting some indications is limited.

Many doctors are cautious about prescribing cannabis. While serious adverse events are rare, there are legitimate concerns around driving, cognitive impairment and drug dependence with products containing delta-9-tetrahydrocannabinol. Cannabidiol-only products pose fewer risks.

**Introduction**

Legal access to medicinal cannabis products is now increasing. Many countries are relaxing their restrictions on cannabis in the face of escalating community interest, commercialisation of products and strong patient demand for access. The vast majority of Australians support access to medicinal cannabis.<sup>1</sup> This support is galvanised by media stories of patients with intractable conditions whose lives have been transformed by cannabis-based medicines.<sup>2</sup>

The medical profession is understandably cautious around medicinal cannabis. A survey of Australian GPs reported that they felt uneducated around access pathways, available products and the evidence base supporting medicinal cannabis.<sup>3</sup> Patient enquiries are common, yet only a small proportion of doctors feel comfortable discussing cannabis with their patients. Overall, GPs are positive about medicinal cannabis prescribing, given sufficient education, particularly for serious conditions such as cancer pain, chemotherapy-induced nausea and vomiting, epilepsy and difficult-to-treat neurological conditions.<sup>3</sup> Specialist colleges and the Australian Medical Association remain conservative voices in the medicinal cannabis debate with concerns around the limited evidence from clinical trials and possible adverse effects.<sup>4,5</sup>

**What is medicinal cannabis?**

The cannabis plant contains hundreds of bioactive molecules, most of which are as yet uncharacterised. The two best studied cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

THC is responsible for the intoxicating effects of cannabis due to its action on CB1 cannabinoid receptors.<sup>6</sup> Despite intoxicating effects at higher doses, clinical trial evidence generally supports the efficacy of THC in treating conditions such as chronic pain, spasticity in multiple sclerosis, anorexia and cachexia, Tourette syndrome and chemotherapy-induced nausea and vomiting.<sup>7,8</sup> Trials currently underway will help to better define the role of THC as a therapeutic across these and other conditions.<sup>9,10</sup>

CBD has a very wide range of pharmacological actions but no intoxicating effects. Early evidence suggests therapeutic actions of CBD at relatively high doses (300–1500 mg) in treating epilepsy, anxiety and psychosis.<sup>11–13</sup> Numerous clinical trials are underway for other conditions such as neuropathic pain, drug and alcohol dependence and neurodegenerative disorders. In many countries, CBD is readily available in over-the-counter nutraceutical ‘wellness’ products. These contain very low doses (e.g. 5–25 mg) for which there is little current evidence of health benefits. Over-the-counter access to CBD is not yet available in Australia, although

the Therapeutic Goods Administration (TGA) is currently examining the possibility of such simplified access.<sup>14,15</sup>

Useful Australian websites on medicinal cannabis are listed in the Box.

## Products

Nabiximols (Sativex) is the only cannabis-based medicine currently listed on the Australian Register of Therapeutic Goods. It is an oromucosal spray containing THC and CBD in a 1:1 ratio and is approved for treating spasticity in multiple sclerosis. Another product, cannabidiol (Epidiolex), is a plant-derived oil-based formulation of CBD. It has recently been approved in the USA and Europe for the treatment of refractory childhood epilepsy, such as Dravet syndrome.<sup>11</sup> The TGA is currently undertaking an expedited review process for registration of this product in Australia.

All other medicinal cannabis products available in Australia are unregistered medicines. Most of these are oral preparations, sprays or capsules of cannabis extracts with only a small fraction involving cannabis plant material such as the flower (intended for vaporisation). The products can contain THC only, CBD only or various ratios of CBD to THC. Around one-third of available products are CBD only.<sup>14,16</sup> Trace levels of other cannabinoids and bioactive compounds (e.g. terpenes) may also be present.

Therapeutic doses of THC (5–20 mg) tend to be much lower than for CBD (e.g. 50–1500 mg). Many combined products therefore contain CBD:THC ratios of 10:1, 20:1 or 50:1.

## Accessing products

Unregistered cannabis-based medicines are accessed through the TGA Special Access Scheme Category B (SAS-B) and the Authorised Prescriber Scheme. The vast majority are via SAS-B, although some prescribing also occurs through the Authorised Prescriber Scheme. The latter grants approval for a doctor to prescribe a specific product to a class of patients, rather than an individual patient (e.g. paediatric neurologists prescribing CBD products for children with refractory epilepsy).

SAS-B and Authorised Prescriber applications can be submitted without cost via the TGA's website. The online portal has a single application which includes any additionally required applications for state and territory health departments, except for Tasmania (see Table). SAS-B applications are typically processed within two days if all the necessary information is provided. The vast majority of these are approved without modification.

Generally, an SAS-B application must state the clinical justification for the use of a specific medicinal cannabis product for a particular patient. This includes the reasons for using an unregistered product rather

## Box Useful websites for information on medicinal cannabis in Australia

- [Therapeutic Goods Administration – Special Access Scheme and Authorised Prescriber portal](#)
- [Therapeutic Goods Administration – Clinical Guidance documents](#)
- [The Office of Drug Control – list of manufacturers and suppliers](#)
- [NSW Health](#)
- [Queensland Health](#)
- [Victoria Health](#)
- [WA Health](#)
- [SA Health](#)
- [Tasmania Health](#)
- [ACT Health](#)
- [NT Health](#)
- [Royal Australian College of General Practitioners position statement](#)
- [Royal Australasian College of Physicians statement](#)
- [Australian Medical Association statement](#)
- [Lambert Initiative](#)
- [Freshleaf Analytics](#)
- [NPS MedicineWise](#)

than a registered medicine. Relevant safety and efficacy data and details of patient monitoring are required.

There is also the option to attach any letters of support or recommendations from other treating specialists involved in a patient's care. Prescribing doctors typically report that the first few SAS-B applications are time consuming but that the process rapidly becomes familiar and routine. The process for prescribing medicinal cannabis in Australia is outlined in Fig. 1.

## Usage

By the end of 2019, more than 18,000 patients in Australia had accessed medicinal cannabis. This prescribing was by more than 1465 medical practitioners, mostly GPs.<sup>14</sup> The number of approvals is rapidly increasing with a total of more than 28,000 individual applications approved as of 31 December 2019.<sup>14</sup> As of June 2020, current approvals are running at around 4500 per month. The difference between the number of patients (18,000) and number of approvals (28,000) reflects repeat applications for the same patients – approvals are usually only provided for one year.

## State and territory regulation

THC-containing products in Australia are included in Schedule 8 (controlled drugs). Prescriptions therefore require approval by a state or territory health department like other Schedule 8 medicines. The Table summarises the current requirements. Products that contain CBD only (at least 98% of total cannabinoid content) are Schedule 4 (prescription-only) medicines and do not require such approvals.

**Table Australian state and territory requirements for prescribing Schedule 8 medicinal cannabis products**

		<b>WA</b>	<b>VIC</b>	<b>NSW</b>	<b>QLD</b>	<b>TAS</b>	<b>NT</b>	<b>ACT</b>	<b>SA</b>
<b>Authorised</b>	General practitioner prescribing	Yes*	Yes	Yes	Yes	No†	Yes	Yes	Yes
	TGA online portal application	Yes	Yes	Yes	Yes	–	Yes	Yes	Yes
<b>Documents required</b>	State Health application	Done simultaneously via TGA online portal	Done simultaneously via TGA online portal	No – unless <16 years of age or a drug-dependent person	No – unless a drug-dependent person	–	No – but required to notify the NT Chief Health Officer if the patient uses a Schedule 8 medicine for >8 weeks	Done simultaneously via TGA online portal	Yes‡ The patient can be put on a 2-month trial (and then health authority approval must be sought), if they are not on any other Schedule 8 medicine or drug dependent.
	Clinical justification and treatment plan	Yes	Yes	Yes	Yes	–	Yes	Yes	Yes
	Cannabis-based consent form	No§	No§	No§	No§	–	No§	Yes	Yes
	Letter of support from specialist	No*#	No#	No#	No#	–	No#	Yes	No#

\* GPs in WA are required to seek specialist approval when prescribing to children under 16 years of age or to drug-dependent individuals.

† Only specialists can prescribe in Tasmania.

‡ Patients over 70 years of age or notified palliative care patients do not need a SA Health Schedule 8 approval.

§ Cannabis-based medicine consent forms are not required, but it is recommended to have one in the patient's records.

# Unless a GP is applying to treat a condition outside of their area of expertise.

TGA Therapeutic Goods Administration

When prescribing for patients located in other states and territories, the prescriber must be mindful of meeting the Schedule 8 authorisation requirements of the location in which the product is dispensed. Tasmania has stringent additional requirements so there are few approvals in that state.<sup>14</sup>

## Dispensing

Medicinal cannabis products are dispensed by pharmacies. It is critically important that the dispensing pharmacist has an understanding of the product and has clear lines of communication with the patient and prescriber. There is often a dose titration during the first weeks of therapy and this needs to be clearly communicated with the patient.

Supply chain problems can prevent access to a product that has been specified in the SAS-B application.

It may then become necessary for a clinical re-evaluation to find a more readily available product and to apply for a new SAS-B permit for that product.

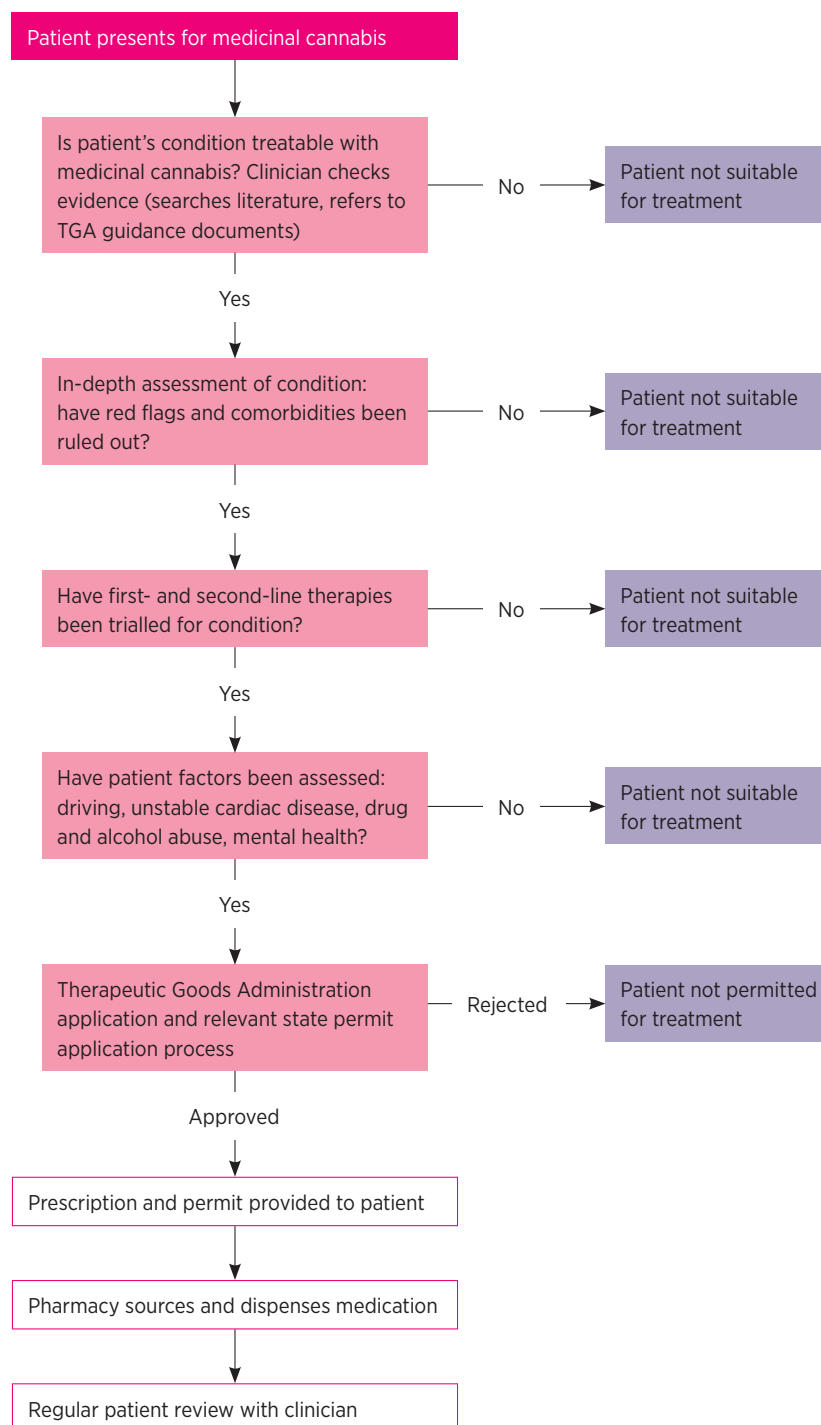
No cannabis products currently have a subsidy on the Pharmaceutical Benefits Scheme and costs can be considerable. These are typically around \$5–\$15 a day,<sup>16</sup> but substantially more for patients with conditions such as epilepsy that require very high doses of CBD. It is important for prescribers to have an open conversation with their patients around likely ongoing costs. Patients receiving disability pensions, aged pensions or other Centrelink benefits may be unable to afford medicinal cannabis.

## Conditions treated

Most approvals under SAS-B are for the treatment of chronic non-cancer pain (Fig. 2). This includes conditions such as arthritis, lower back pain, neck pain and various forms of neuropathic pain. These are typically treated with oral solutions that contain THC and sometimes additional CBD. Other common conditions among SAS-B approvals include anxiety, cancer-related symptoms (e.g. pain, nausea, anorexia), epilepsy, insomnia, and spasticity in multiple sclerosis (Fig. 2). CBD-only products are being used in all of these conditions, but there is a greater use of them in patients with epilepsy and anxiety. The anxiolytic effects of CBD are described in the literature.<sup>13,17,18</sup>

The TGA has published a series of clinical guidance documents that summarise the available evidence for medicinal cannabis products in chronic pain, palliative care, epilepsy, spasticity in multiple sclerosis and chemotherapy-induced nausea and vomiting. However, definitive evidence in support of specific medicinal cannabis products for various conditions is often not available. This absence of evidence reflects historical difficulties in undertaking clinical

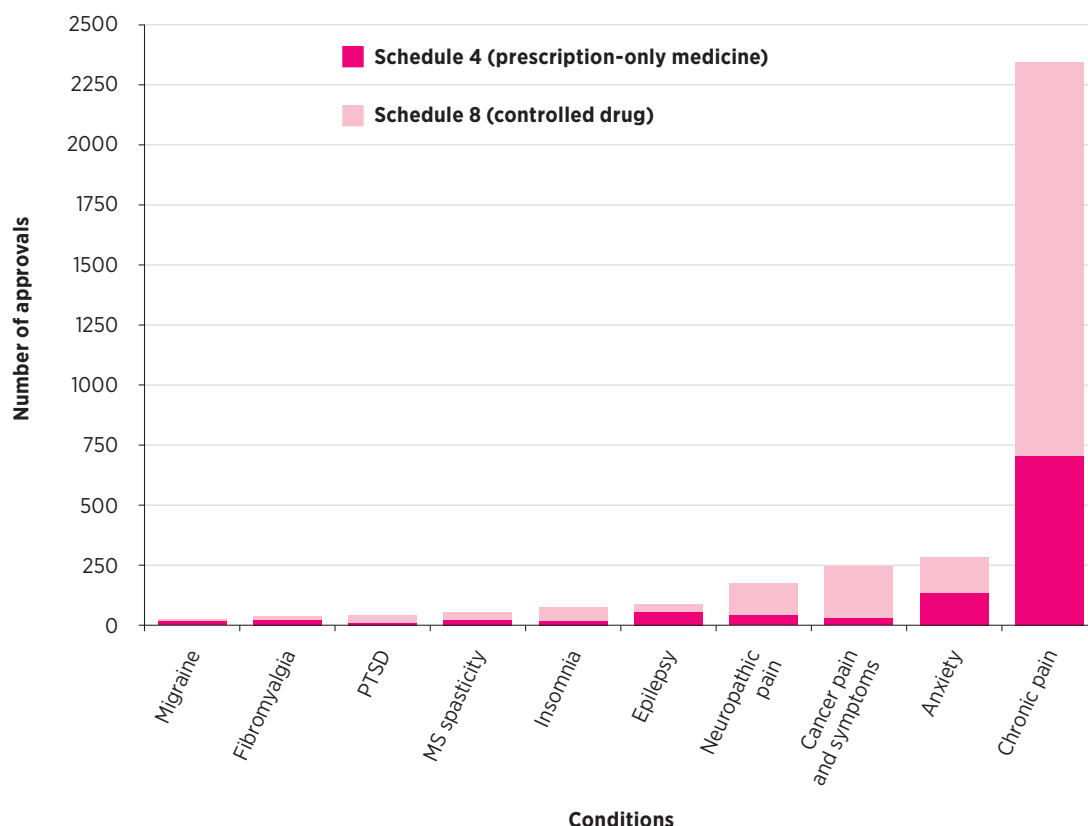
Fig. 1 How to prescribe medicinal cannabis in Australia



trials with cannabis products<sup>7</sup> and the recency with which CBD has been identified as a therapeutic drug. Nonetheless, TGA assessments under SAS-B appear to give the benefit of the doubt with regard to evidence. SAS-B approvals have been given for conditions such as autism, insomnia and movement disorders despite a lack of compelling supportive evidence.



Fig. 2 Approvals for medicinal cannabis products in October 2019\*



PTSD post-traumatic stress disorder

MS (multiple sclerosis) spasticity includes approvals for MS spasm, pain and spasticity.

Epilepsy includes approvals for epilepsy, seizure and psychogenic seizures.

Neuropathic pain includes approvals for neuropathic pain and peripheral neuropathy.

Anxiety includes approvals for anxiety and social anxiety disorder.

\* Data are for 3364 approvals under Special Access Scheme Category B. Sourced from Freedom of Information Request #1409 to the Therapeutic Goods Administration.

## Adverse effects

It is recommended that medical practitioners discuss with their patients the risks and benefits of medicinal cannabis so that the patient can provide informed consent to this therapeutic pathway. Patients need to be given information about common and serious adverse effects. Cannabis, THC and CBD are generally well tolerated by patients with few serious adverse effects.<sup>6,19-22</sup> At higher doses, THC can have sedative effects and make naïve users feel dizzy and 'spaced out'.<sup>6,19-22</sup> Appetite stimulation ('the munchies') is also common with THC.<sup>6</sup> A typical intoxicating dose of THC in a naïve user is at least 10 mg, although some patients may be more sensitive. Starting low and slowly titrating the dose upwards is the best practice. The more troubling symptoms of THC intoxication, such as paranoia, severe anxiety and psychotic reactions,

can be minimised with careful titration and also by combining with CBD which may have antipsychotic and anxiolytic effects. Regular review of patients is recommended.

CBD has been shown to be well tolerated at very high doses (up to 5000 mg).<sup>23</sup> CBD is a potent inhibitor of various cytochrome P450 enzymes.<sup>24,25</sup> Higher doses may increase plasma concentrations of anticonvulsant drugs such as clobazam and topiramate.<sup>26</sup> Children with epilepsy who are on concomitant anticonvulsant drugs may be vulnerable to related adverse effects such as sedation, gastrointestinal upset and elevated liver transaminase levels.<sup>11,27</sup> In clinical trials outside of childhood epilepsy the only significant side effect with CBD was diarrhoea.<sup>27</sup> Interactions of CBD with drugs such as benzodiazepines, antidepressants and opioids appear unlikely to be clinically significant in adult clinical populations, but more research

is required. Given this uncertainty, upwards dose titration is a valid precautionary practice in patients given CBD-containing products, particularly if they are also taking other medicines.

### Effects on driving

Driving is a key issue to discuss with patients as it is currently illegal to drive while being treated with products containing THC. At present in Australia, if THC is detected in oral fluid by mobile drug testing, patients can be prosecuted. There is currently no exemption for people with a legitimate prescription for THC. There is however evidence suggesting that driving impairment is modest in those who repeatedly use THC.<sup>28,29</sup> Current tests can detect cannabis for several hours after THC consumption, but there are large individual differences so some patients are more vulnerable to a positive test than others.<sup>30</sup> Patients should wait at least six hours after consuming THC-containing products before driving and be aware that, even then, they remain vulnerable to prosecution under current laws. Issues associated with workplace use of THC-containing products also need to be carefully considered, especially for patients working in transportation industries and in workplaces requiring the safe operation of heavy machinery.

CBD is not intoxicating. There are no restrictions around driving while taking CBD-only products. THC contamination of CBD products is a significant worldwide issue and it is therefore prudent for doctors and patients to request certificates of analysis from the manufacturer.<sup>31</sup>

### Withdrawal

Cannabis is euphorogenic and can be habit-forming, leading to dependence in approximately 10% of recreational users. Sudden withdrawal can cause a clinically significant but relatively benign withdrawal syndrome that includes mild sleep and appetite disturbances, cannabis craving and emotional lability.<sup>32</sup> The likelihood of drug-seeking behaviour in patients wishing to use medicinal cannabis products should be carefully assessed by prescribers. Patients using higher doses of THC are best gradually titrated off THC-containing products when discontinuing their use. Withdrawal from CBD does not appear to be associated with any significant discontinuation syndrome.<sup>33</sup>

### Current and future challenges

Prescribing medicinal cannabis may feel like a 'leap in the dark' for many GPs who feel uneducated in this emerging area of clinical practice. Australian doctors are fielding daily enquiries about medicinal cannabis from their patients, so it is prudent to learn more regardless of whether they wish to prescribe cannabis

or not.<sup>3</sup> There are educational events, online courses and accredited workshops such as those by the Royal Australian College of General Practitioners. Doctors who do not want to prescribe may wish to direct their patients to one of the many clinics specialising in cannabis access that have been established in many Australian capital cities.

Despite the exponential rise in approvals under the SAS-B scheme, surveys suggest that many Australians continue to self-medicate with illicit cannabis.<sup>34,35</sup> Indeed, the National Drug Strategy Household Survey recently reported that 600,000 Australians use cannabis for medicinal purposes, but only 3.9% obtain it via legal pathways.<sup>36</sup> The reasons for this may include the high cost of unregistered cannabis-based products compared to illicit cannabis (which is often home-grown), the inability to find a doctor who will assist in making an application to the TGA, lack of knowledge of official access pathways, and a reticence to discuss cannabis use with a doctor.<sup>34,35</sup>

Illicit cannabis products are likely to be suboptimal as therapeutics. They probably contain a great deal of THC and little CBD<sup>37</sup> and may also contain contaminants such as pesticides and heavy metals. Artisanal cannabis oils used in Australia to treat intractable childhood epilepsies have pronounced variation in their cannabinoid composition. In some cases, products that were purported to be CBD-dominant were actually rich in THC.<sup>38</sup> Products obtained through official schemes must abide by the Australian standard TGO 93 for medicinal cannabis.

While there is an intent to enable access to quality-controlled medicines via the SAS-B and Authorised Prescriber schemes, the current framework remains a work in progress. It is arguably still short of meeting community expectations around access for patients. A recent Australian Senate Inquiry<sup>14</sup> has offered numerous recommendations for improving patient access to products, as well as identifying strategies to improve the education of doctors in this rapidly developing and sometimes challenging area of clinical practice. ◀

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## ARTICLE

## Prescribing medicinal cannabis

Iain McGregor is Academic director of the Lambert Initiative for Cannabinoid Therapeutics. He has served as an expert witness in various medicolegal cases involving cannabis, has received honoraria from Janssen, is currently a consultant to Kinaxis Therapeutics, and has received research funding and fellowship support from the Lambert Initiative, NHMRC and Australian Research Council. He holds a variety of patents for non-cannabinoid therapeutics.

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## ARTICLE

# A stain on iron therapy

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**Keywords**

ferric carboxymaltose, injection site reaction, iron staining, laser therapy

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**SUMMARY**

Iron staining is an unwanted and in some cases permanent adverse effect of intravenous iron administration. Cosmetically unacceptable staining may cause distress and have psychological implications for the patient.

There should be a suitable indication for parenteral iron therapy. Patients must be advised of the risk of harm and give their informed consent before receiving parenteral iron.

Strategies to minimise the risks of staining with intravenous iron include appropriate cannulation and close monitoring of the infusion. Stop the infusion if there are signs of extravasation.

Laser therapy may be a treatment option in cases of persistent discolouration due to iron staining.

**Introduction**

Iron deficiency is a common condition and a large contributor to anaemia.<sup>1</sup> The prevalence of iron deficiency anaemia is high in younger women and indigenous Australians.<sup>2</sup> Treatment options to correct iron deficiency in Australia include oral and parenteral iron.<sup>3</sup> Within the last decade the use of intravenous iron has been increasing,<sup>4</sup> particularly in the community. This is because of newer iron salts with favourable adverse effect profiles and shorter infusion times for intravenous formulations. These include ferric carboxymaltose and ferric derisomaltose. For patients in hospital, iron polymaltose or iron sucrose can also be used.

An uncommon adverse effect of parenteral iron is skin staining (see Fig.). This is not a new phenomenon as it is a well-known adverse effect of intramuscular iron.<sup>5</sup> Iron staining can occur with intravenous infusions if there is extravasation into the surrounding tissue. The use of intramuscular iron administration

is limited in practice,<sup>3</sup> but the injection can be given into an unexposed site. However, administration at an unexposed site is not necessarily possible when giving iron intravenously. A rise in reports of iron staining<sup>6–10</sup> may correspond with the increasing use of intravenous iron in clinical practice.<sup>6–13</sup>

**Incidence of skin staining**

The rate of skin discolouration with intravenous iron preparations has been reported in clinical trials as 0.68%<sup>14</sup> to 1.3%.<sup>15</sup> Postmarketing reports suggest the incidence may be lower and skin necrosis has not been reported. However, iron staining may be under-reported to pharmacovigilance databases. A review of the French pharmacovigilance database from 2000 to 2016 found only 51 cases of cutaneous pigmentation with iron.<sup>12</sup>

Postmarketing reports to the Therapeutic Goods Administration (TGA) Database of Adverse Event Notifications,<sup>16</sup> from March 2014 to October 2019, included 27 cases for ferric carboxymaltose. These reports included the terms skin discolouration or hyperpigmentation, haemosiderin stain, pigmentation disorder, infusion/injection/administration site discolouration, or extravasation. The TGA data include eight cases of pigmentation disorder or skin discolouration with iron polymaltose, with the first report in 2005. There are currently no reports for ferric derisomaltose, but this adverse effect is included in the product information.

**Minimising harm**

Specific definitive risk factors for extravasation of intravenous iron have not been published. The principles for minimising the harm associated with intravenous iron preparations have been adapted from those applied to intramuscular iron (Box 1).<sup>5</sup> They include a good infusion technique (Box 2).

**Fig. Iron stain**





### Box 1 Principles for minimising the risk of intravenous iron stains

- Ensure an appropriate indication for parenteral iron
- Inform the patient of the risk of skin staining at the initial consultation
- Ensure the correct injection site and administration technique is used
- Monitor closely for signs and symptoms of extravasation

### Is parenteral iron indicated?

Once iron deficiency is diagnosed, establish the cause. The decision on appropriate treatment should then consider the patient's treatment goals. This includes assessing the options for correcting the iron deficiency and their potential adverse effects. Dietary intake, oral supplements or parenteral iron are suitable options.<sup>3</sup>

Parenteral iron is usually only indicated when oral iron therapy has failed.<sup>3</sup> However, there are some patient cohorts who may benefit from intravenous iron without a trial of oral therapy. They include patients who have heart failure with a reduced ejection fraction,<sup>15</sup> those undergoing haemodialysis,<sup>17</sup> and pregnant women in their second or third trimester requiring rapid iron replenishment.<sup>18</sup>

### Inform patients about skin staining

Although the incidence of iron staining appears to be relatively low, its potential irreversibility and the cosmetic impact it may have warrant discussion with patients. The Medical Board of Australia has reminded medical practitioners to advise patients about the risk so that they can give informed consent to treatment.<sup>19</sup> Using a patient information brochure about iron staining may assist with this. The BloodSafe organisation has a useful leaflet available in English and other languages.<sup>20</sup> When intravenous iron is indicated and patients choose to receive an infusion, it is advisable to document the content and outcome of the discussion about risks including discolouration or staining.

### Correct injection site and infusion technique

The infusion sites used for intravenous therapy may influence the rate of extravasation due to the potential for vessel damage related to movement of the cannula.<sup>21,22</sup> Administration of intravenous iron via cannulation at sites of flexion (e.g. antecubital fossa, wrist) or on the back of the hand should be avoided when possible. If these sites must be used, the smallest suitable cannula size may reduce the likelihood of vessel trauma.<sup>22</sup> Try to minimise catheter movement by securing the cannula<sup>21-23</sup> and using an

### Box 2 Infusion technique to minimise the risk of iron staining

- Avoid intravenous iron administration via cannulation at sites of flexion (e.g. antecubital fossa, wrist) or on the back of the hand
- The distal veins of the forearm are the preferred site
- Use an appropriate cannula size (20- to 24-gauge)
- Secure the cannula and use an extension set to minimise catheter movement
- Do not cover the injection site with a bandage
- Minimise the number of cannulation attempts
- Ensure the patency of the vein before administration. If patency is uncertain, do not administer intravenous iron
- Do not give infusions at night-time
- Do not give infusions to patients unable to report symptoms (e.g. anaesthetised)

extension set.<sup>24</sup> When using smaller gauge devices, it may be necessary to slow the infusion to minimise the risk of dislodgement.<sup>25</sup>

The number of attempts at cannulation should be minimised as there is an increased risk of extravasation due to multiple venous punctures.<sup>21,22</sup> For patients who are difficult to cannulate, seek the expertise of more experienced staff. Although postponing intravenous iron therapy may inconvenience the patient, it is unlikely to result in adverse clinical outcomes. Intravenous iron infusion is rarely urgent.

The patency of the cannula should be checked by giving 5–10 mL of sodium chloride 0.9% before the infusion.<sup>21</sup>

### Monitor for extravasation

The review of cutaneous pigmentation reported to the French pharmacovigilance database suggested improvements in monitoring are necessary to detect extravasation.<sup>12</sup> Patients who experience iron extravasation resulting in staining may describe pain, swelling, and feelings of pressure or pricking at the infusion site.<sup>13</sup> Patients should therefore be told to notify staff of any of these symptoms (Box 3). This is an important consideration for patients who do not understand English. Administration of intravenous iron must be avoided if the patient's ability to report these symptoms is reduced (e.g. anaesthetised patients). Early cessation of the infusion may limit the amount of solution that enters the tissues and could minimise the extent of staining.

Close assessment of the cannula site during infusion is essential to enable early identification of extravasation. The site should never be covered up with a bandage. Observations of the cannula site should be timed to correspond with monitoring of the patient's other

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vital signs in accordance with local protocols for infusions.<sup>26</sup> Giving intravenous iron infusions overnight must be avoided as it is more difficult to observe extravasation and staining in the dark.

### Staff training

In order to ensure the best outcomes for patients, health professionals involved with the prescribing, administration and monitoring of intravenous iron must be adequately trained and competent. A set protocol that outlines best practice for intravenous iron administration, including cannulation, should be followed. Staff must be aware of the monitoring requirements and the symptoms of potential adverse effects.

### Management of iron staining

There are no published guidelines outlining how to manage iron extravasation or skin discolouration following iron infusions. Box 4 gives the best available guidance for acute management to limit the potential for further staining. Clinical photographs should also be taken to capture the extent of the extravasation and to help with monitoring the success of subsequent treatments.

There are limited options to reverse iron staining. Topical therapies, lymphatic drainage and massages have been tried without success.<sup>9,13</sup> The most evidence for successful reversal of iron staining is with laser therapy.

One review assessed 29 patients who had reported accidental staining from iron infusions over a nine-year period.<sup>13</sup> Thirteen patients had laser therapy

and eight completed treatment. Regression of iron staining took an average of 5.6 laser sessions over one to two years. The type of laser is important with most evidence being for quality-switched Nd:YAG or picosecond. The patient's individual skin type may also influence the success of laser treatment. In general, laser therapy was well tolerated.

Laser therapy is available in Australia, but there may be significant financial barriers as repeated applications are required. If the patient is concerned about the staining, early referral to a dermatologist with a laser clinic specialising in quality-switched Nd:YAG and picosecond laser is appropriate.

### Review cases to improve patient safety

When extravasation occurs, prudent review of the patient is warranted. Consider likely contributing factors, such as whether there was a suitable indication for intravenous iron, poor techniques in cannulation, the patient's own vasculature and any lack of monitoring. Report these cases to the TGA.

### Conclusion

There should be a clear indication for using intravenous iron. Patients need to give informed consent for the infusion.

Iron extravasation can be cosmetically unacceptable for patients so strategies should be put in place to prevent it from occurring. These include appropriate vein selection, securing the cannula and close monitoring during the infusion. In addition, the patient should be advised to report any pain, irritation or swelling at the infusion site.

In the event of extravasation and persistent staining, repeated laser sessions over one to two years may be required. However, iron staining can be permanent. ◀

#### Box 3 Clinical features of iron extravasation<sup>6-13</sup>

##### Symptoms during infusion

Pain, swelling, feeling of pressure, prickling on the injection site and immediately observable staining. Note: some patients report no pain or other symptoms during the infusion and the discolouration appears hours or days later

##### Extent of skin discolouration

Can be localised to around the injection site or extend along the length of the arm. May be patchy or consistent discolouration

##### Colour changes

Most common – light to dark brown

Less common – black, bluish, purple, grey

##### Symptoms in the longer term

Generally, discolouration is asymptomatic, but some patients complain of aching, changed sensitivity in the affected area or tenderness on palpation

##### Outcome

In many cases, iron staining is permanent. Some patients report fading of the stain over time or successful treatment with laser therapy

#### Box 4 Acute management of iron extravasation

If the patient complains of pain, swelling, soreness at the injection site or there is any obvious swelling or discolouration, stop the infusion immediately and assess the site

Disconnect the giving set

Aspirate any residual drug from the cannula

Remove the cannula

Apply a cold pack if there is swelling or soreness, however this does not appear to prevent the spread of the stain

Conflict of interest: none declared

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## SELF-TEST QUESTIONS

True or false?

- Extravasation of intravenous iron leads to skin necrosis
- The skin staining from intravenous iron usually resolves in one week

Answers on page 179

## ARTICLE

# Real-time prescription monitoring: helping people at risk of harm

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**Keywords**

opioid addiction, prescription drug monitoring programs, substance-related disorders

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**SUMMARY**

Misuse of opioid analgesics and other psychoactive medicines is a serious and increasing problem in Australia. Measures are being taken to try and prevent this progressing to a public health crisis like the opioid overdose epidemic seen in the USA.

One measure is real-time prescription monitoring. This provides real-time information about the patient's supply of psychoactive medicines which have a high risk of being misused.

Having identified a patient at risk, many factors may delay appropriate management or result in the patient being discharged from care. These factors include subconscious negative stereotyping, a focus on preventing 'doctor shoppers' diverting psychoactive medicines, and a fear of sanction by regulators.

The Medical Board of Australia provides guidance about good practice. Patients should be treated with respect, free from bias and discrimination, and without prejudicing care because of the belief that their behaviour has contributed to their problems.

**Introduction**

Misuse of opioid analgesics, benzodiazepines and other psychoactive medicines is a serious and increasing problem in Australia. Since 1999 thousands of Australians have died from an opioid overdose.<sup>1</sup> New strategies and tools have been developed to manage this risk and help clinicians ensure the safe use of high-risk drugs.

Many deaths involve people obtaining multiple prescriptions from multiple healthcare providers. Some deaths might be prevented if information about the supply of high-risk drugs is available to health professionals at the time of prescribing. This can be provided by new Australian real-time prescription monitoring systems. While this may prompt management of the patient's drug use, there could be unintended consequences.

**Patients with multiple healthcare providers**

Real-time prescription monitoring may identify high daily doses of opioids, high-risk combinations and patients with multiple prescribers whose treatment is not coordinated. The risk of overdose increases if supply is not coordinated.

Patients with multiple providers are a heterogeneous group. They range from patients with approved indications taking recommended doses, patients with an iatrogenic addiction who are unaware that they are at risk, and those deliberately and fraudulently

seeking psychoactive medicines for their intoxicating effect or for trafficking.<sup>2</sup>

Trust is basic to the doctor–patient relationship. When this is exploited by a drug-seeking person it may cause negative feelings and indiscriminate refusal to continue treatment for other patients assumed to be fraudulently seeking prescriptions. The focus on preventing 'doctor shoppers' may influence this attitude but, like any other medical condition, patients with multiple providers will benefit from a patient-centred approach.

**Escalating opioid prescribing**

There was a 15-fold increase in the supply of prescription opioids between 1992 and 2012.<sup>3</sup> During this time several new, potent opioids and many new formulations were marketed in Australia. Approximately three million Australians now use opioids each year. About 2.5 million report lifetime non-medical use of pharmaceutical drugs. In 2016 more than 700,000 Australians used opioid analgesics non-medically to achieve a drug effect.<sup>4</sup>

Every day there are nearly 150 hospitalisations, 14 emergency department presentations and three deaths involving opioids.<sup>5</sup> Increasing numbers of people are being treated in alcohol and drug clinics or being prescribed medicines to treat pharmaceutical opioid dependence.

Opioids and benzodiazepines are commonly involved in overdose deaths. Non-medical use of opioid

analgesics predisposes some people to transition to heroin or other illicit opioids.<sup>6</sup> Further vulnerability and risk can emerge from concomitant mental health disorders.

The USA is experiencing a public health crisis due to an epidemic of opioid overdoses. Since 1999 there have been more than 400,000 deaths from opioid overdose with 47,600 in 2017 alone.<sup>7</sup> Between 8 and 12% of patients with chronic pain may be addicted to opioids.<sup>8</sup> It is conceivable that, without action, the same problems could occur in Australia.

### Real-time prescription monitoring

Australian governments are developing strategies to prevent harm from misuse of prescription opioids.<sup>9</sup> One strategy was to reschedule analgesics containing codeine from being available over-the-counter to Schedule 4, requiring a prescription for supply.<sup>10,11</sup> The states and territories are now introducing real-time prescription monitoring. This provides the prescriber with an up-to-date history of the patient's supply of high-risk psychoactive medicines to help identify those with an established or emerging problem.<sup>12</sup>

### Risk and bias

Real-time prescription monitoring will change clinical practice but could have unintended effects.<sup>13</sup> Authors of a study of mortality after discontinuation of opioid therapy suggested that these deaths could reflect interruption of other medical care, loss of tolerance, or destabilisation of an underlying opioid use disorder.<sup>14</sup> Primary care is well-placed to manage substance use disorder, but without support many GPs are reluctant to take on new patients being treated with opioids<sup>15</sup> or to prescribe opioid substitution therapy.<sup>16</sup> They may indiscriminately discharge patients with problems identified by real-time prescription monitoring from their practice.<sup>17</sup>

This reluctance to manage opioid addiction may develop because of:

- lack of time, confidence, or training in managing substance misuse (practitioners are more confident managing smoking than other substance use disorders)
- negative experiences with drug-seeking individuals or illicit drug users<sup>16</sup>
- stigma associated with substance misuse and dependence,<sup>18</sup> as patients with substance use disorder are stereotyped as being dangerous or unpredictable, having a character weakness or moral problem, and being blameworthy for their condition<sup>19</sup>
- fear of sanction from regulatory authorities, such as professional registration boards.

Prevailing negative stereotypes are passively absorbed, causing subconscious bias and discrimination. During their undergraduate and early careers health professionals see a biased sample of people with substance use disorder – homeless and intoxicated people with alcohol or drug problems, or people injecting illicit drugs who may be hostile and aggressive. They are less exposed to professional and business people who misuse drugs. However, many patients at risk will be identified by real-time prescription monitoring. Whatever their background, all people need and deserve treatment that may prevent ongoing and serious harm, including death from overdose.

Patients who have become dependent on drugs prescribed by their doctors often differ from illicit drug users. Those iatrogenically addicted may respond more favourably to treatment. They are often highly functioning, with more social supports, higher levels of education, more likely to be employed with fewer legal problems and are not connected to illicit drug markets.<sup>20,21</sup> These patients feel that they are more socially and economically active<sup>22</sup> and unsuited to treatment in drug and alcohol clinics. However, some of them will also use illicit drugs. These patients are at heightened risk of serious harm and will need treatment tailored to their circumstances.

Pre-existing bias is often exacerbated by public and professional media, indemnity insurers, and other communications that focus on preventing the diversion of psychoactive medicines by 'doctor shoppers'. This focus may promote a climate of enforcement or policing of psychoactive medicine supply instead of identifying patients at risk and in need of treatment.

### Possible unintended consequences

Activities intended to prevent harm can result in unintended consequences if they are not supported by the right clinical approach.<sup>13</sup> For example, abrupt cessation of opioids can have serious adverse effects.

The tapering of opioid doses requires special care, especially given that many patients taking opioids have a history of mental health disorder or substance use disorder.<sup>23</sup> Patients rapidly or involuntarily tapered from opioids may have an increased risk of overdose so discussions of risk and ensuring patient agreement before tapering starts are high priorities.<sup>24</sup>

In 2016 the US Centers for Disease Control published evidence-based guidelines about the use of opioids for chronic pain<sup>25</sup> that recommended caution with the dose and duration of opioid therapy. Misapplication of these dosing guidelines exposed patients to involuntary and abrupt tapering of opioid doses



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Real-time prescription monitoring: helping people at risk of harm

without being offered alternative treatment.<sup>26</sup> Patients experienced increases in pain and distress, and mental health problems such as depression, with some turning to suicide. Many clinicians and organisations voiced their concerns,<sup>27</sup> including that patients might be forced to seek opioids elsewhere, including the illicit opioid market.<sup>28</sup> The US Department of Health and Human Services responded with guidance about tapering that promoted a cautious, respectful approach to tapering, and advocated active agreement of patients in the decision to taper, and consideration and treatment of comorbid mental health disorders. Rapid tapering was to be avoided in most circumstances.<sup>23</sup>

Primary care providers in the USA describe difficulties in discussing the findings of prescription monitoring programs with patients and sometimes avoid talking about these findings.<sup>29</sup> Some health professionals in New York State responded to the mandatory use of a prescription monitoring program by using it to purge their practices of 'deceptive' or 'bad' patients, rather than as a method of identifying patients who needed professional help and setting them on the path to recovery.<sup>30</sup>

### How to respond

The use of the term 'doctor shopper' suggests all people with multiple prescribers are drug-seeking for non-medical purposes. There is a need to help each patient according to their individual circumstances and avoid this stigmatising language that prejudices patients.

A patient-centred approach to opioid use<sup>31</sup> focuses on the patient's understanding of their situation

and the underlying cause and its effects on daily functioning. Ask how they would prefer to manage it and offer realistic options consistent with professional responsibilities to provide safe care,<sup>32</sup> including referral for, or treatment with, methadone or buprenorphine if appropriate (see Box).<sup>33</sup>

Specialist telephone alcohol and other drug advisory services are available to support health professionals in most states and territories.<sup>34</sup>

The Medical Board of Australia provides guidance about good medical practice. This should be applied to the care of patients with multiple providers as much as any other patient. Care should be respectful, free from bias and discrimination, and needs to avoid prejudices because of the belief that the patient's behaviour has contributed to their condition.<sup>35</sup>

### Conclusion

The relief of suffering is one of the guiding principles of clinical practice. Patients with opioid addiction are a heterogeneous group and it is important to determine the circumstances of each individual so that a professional response can be tailored to their needs.

Clinical practice constantly evolves, changing as evidence of more effective treatments emerge. Real-time prescription monitoring will identify people not previously known to have a substance-related disorder. There is a need to avoid unfairly stigmatising these patients and to act to provide potentially life-saving treatment. ◀

*Conflict of interest: none declared*

#### Box How to respond when real-time prescription monitoring finds a patient has obtained psychoactive medicines from other providers

It is essential to determine the underlying motivation of behaviour by people with multiple healthcare providers, to respond appropriately and avoid indiscriminate refusal of care for vulnerable patients.

Assess whether the problem is one of substance use disorder and, if so, offer referral or treatment as the sole prescriber.

Frame discussions as an expression of concern about the patient's safety and the need to coordinate treatment with high-risk drugs.

Avoid using the stigmatising term 'doctor shopper'.

1. Discuss the finding and confirm with the patient that the real-time monitoring is correct. If the patient denies attending a particular provider, contact that provider to establish whether or not they prescribed.
2. Assess whether there is a reasonable explanation for obtaining drugs from other prescribers and explain that for safety reasons there is a need to know every time drugs are prescribed by other providers.
3. Assess whether the dose is appropriate for their clinical need.
4. Either continue treatment as the patient's sole prescriber, or arrange referral to their preferred prescriber. Communicate this arrangement with that provider through the contact details included in the patient's monitoring record.
5. If there are concerns about diversion or misuse, discuss this, assess the clinical need and suggest a urine drug screen. If appropriate, offer a short-term supply, then review the results of the urine drug screen and real-time prescription monitoring at the next consultation.

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## ARTICLE

# Harms and benefits of sodium-glucose co-transporter 2 inhibitors

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## SUMMARY

Sodium-glucose co-transporter 2 inhibitors are oral glucose-lowering drugs that increase the urinary excretion of glucose. In patients with type 2 diabetes and cardiovascular disease they reduce all-cause mortality, cardiac mortality, rates of hospitalisation for heart failure and the progression of renal disease.

There are adverse effects related to the mechanism of action. These include polyuria and intravascular volume depletion from osmotic diuresis, and genitourinary infections from glycosuria. Ketoacidosis is a rare adverse effect.

The glucose-lowering efficacy of sodium-glucose co-transporter 2 inhibitors decreases with increasing renal impairment.

## Introduction

The Australian Therapeutic Goods Administration (TGA) first approved sodium-glucose co-transporter 2 (SGLT2) inhibitors in 2013. There are now three SGLT2 inhibitors listed on the Pharmaceutical Benefits Scheme (PBS). They are available individually or in combination with other drugs, such as metformin (Table).

## Mechanism of action

Each day the kidneys normally filter about 180 g of glucose, but over 90% is reabsorbed in the proximal renal tubule. This reabsorption is facilitated by SGLT2. Inhibiting this transporter reduces the renal threshold for glucose excretion, causing glycosuria.

SGLT2 inhibitors have a glucose-lowering effect which is independent of the insulin concentration or insulin

resistance. They also have a diuretic effect. As there is a caloric loss of glucose in the urine, the drugs cause a small amount of weight loss.

The glucose-lowering effect depends on functioning renal tubules, so the efficacy of SGLT2 inhibitors reduces with increasing renal impairment. According to the product information, all three PBS-subsidised SGLT2 inhibitors are contraindicated when the estimated glomerular filtration rate (eGFR) is persistently below 45 mL/min/1.73 m<sup>2</sup>. This may change in the future as recent studies have shown benefits in patients with a lower eGFR.<sup>1–3</sup>

SGLT2 inhibitors increase ketone concentrations and ketone production. The precise mechanism is unclear. It may be due to an increase in the glucagon:insulin ratio leading to lipolysis, proteolysis, gluconeogenesis and ketone formation as well as modest intravascular volume contraction and increased renal reabsorption of ketones.<sup>4</sup>

## Benefits

The glucose-lowering effect of SGLT2 inhibitors is comparable to that of other oral drugs for diabetes. Glycated haemoglobin (HbA1c) is reduced by 0.5–1% compared to placebo.<sup>5,6</sup> Greater HbA1c reductions are seen in patients with higher baseline HbA1c concentrations.<sup>7</sup>

SGLT2 inhibitors do not usually cause hypoglycaemia except when taken with insulin or sulfonylureas.<sup>8</sup> Caloric loss from glycosuria leads to a mean weight loss of 2.5 kg at one year.<sup>5</sup> SGLT2 inhibitors have a small but favourable effect on blood pressure. On average they lower systolic pressure by 4 mmHg and diastolic pressure by 1.6 mmHg.<sup>9</sup>

**Table SGLT2 inhibitors listed on the Pharmaceutical Benefits Scheme**

Generic	Brand names	Approved total daily dose
Dapagliflozin	Forxiga Xigduo XR (dapagliflozin + modified-release metformin)	10 mg
Empagliflozin	Jardiance Jardiamet (empagliflozin + metformin) Glyxambi (empagliflozin + linagliptin)	10 mg or 25 mg
Ertugliflozin	Steglatro Segluromet (ertugliflozin + metformin) Steglujan (ertugliflozin + sitagliptin)	5 mg or 15 mg

Empagliflozin was studied in the EMPA-REG OUTCOME trial. This randomised controlled trial included over 7000 patients with type 2 diabetes and established cardiovascular disease. Those treated with empagliflozin had significantly lower rates of death from cardiovascular causes (38% relative risk reduction).<sup>10</sup> This was a surprise finding of the trial which had been designed to show a lack of cardiovascular harm. A meta-analysis of the three major cardiovascular outcome trials of empagliflozin, canagliflozin and dapagliflozin found a 15% relative risk reduction in all-cause mortality and a 30% relative risk reduction in hospitalisation for heart failure.<sup>11</sup> However, the recently reported cardiovascular outcomes trial of ertugliflozin (VERTIS CV) failed to show a benefit above placebo with no significant reduction in the combined primary outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.<sup>12</sup> This does therefore question whether the cardiovascular benefits are a whole-of-class effect. The SGLT2 inhibitors are beneficial in mild to moderate renal disease. While a transient decrease in eGFR can occur at the start of treatment this is not progressive. It is similar to the decreased eGFR seen when starting an ACE inhibitor.<sup>8</sup> In patients with an eGFR close to 45 mL/min/1.73 m<sup>2</sup> a drop to below 45 mL/min/1.73 m<sup>2</sup> may be seen, however this is anticipated and not a reason to discontinue therapy. In the long term SGLT2 inhibitors are renoprotective, with a 45% relative risk reduction in the progression of renal disease (worsening eGFR, end-stage renal disease or renal death) compared to placebo.<sup>11</sup>

## Adverse effects

Some of the adverse effects can be predicted from the mechanisms of action of the SGLT2 inhibitors.

### Genitourinary infections

SGLT2 inhibitors are associated with 3–5-fold increased risk of fungal genital infections (such as candidiasis).<sup>13</sup> The infections occur more commonly in women and are generally mild. They may be treated with antifungal therapy and usually do not require the SGLT2 inhibitor to be stopped. Patients at higher risk include those with previous genital candidiasis and uncircumcised men.<sup>14</sup>

Some studies have found an association with urinary tract infections. However, recent meta-analyses have not found a relationship between infections and SGLT2 inhibitors, except for dapagliflozin.<sup>13,15</sup>

Nonetheless, there have been postmarketing reports of pyelonephritis and complicated urinary tract infections in patients taking SGLT2 inhibitors.<sup>14</sup>

There have been case reports and case series of necrotising fasciitis of the perineum (also known

as Fournier's gangrene) associated with SGLT2 inhibitors.<sup>16</sup> However, in the dapagliflozin and cardiovascular outcomes in type 2 diabetes trial (DECLARE-TIMI 58) involving 17,160 patients there were five cases of Fournier's gangrene in the placebo group and only one in the dapagliflozin group.<sup>17</sup> Furthermore, a meta-analysis of randomised controlled trials with over 69,000 patients in total found no increase in rates of Fournier's gangrene. Due to the small number of total events, this meta-analysis was unable to completely exclude an increased risk.<sup>18</sup>

### Volume depletion

SGLT2 inhibitors are associated with a small increase in adverse effects related to intravascular volume depletion, such as hypotension, syncope and dehydration.<sup>14</sup> In euvoelaemic patients consider reducing the dose of any diuretics to avoid further volume depletion. SGLT2 inhibitors should be withheld when a patient is at risk of dehydration, such as during an episode of gastroenteritis, when systemically unwell and around medical and surgical procedures.

### Ketoacidosis

SGLT2 inhibitors have been associated with an increased risk of diabetic ketoacidosis. A South Australian case series identified 13 cases of diabetic ketoacidosis over a 15-month period.<sup>19</sup> Precipitants included missed insulin, undiagnosed type 1 diabetes, infection, fasting, and low-carbohydrate diets.<sup>19</sup> A Victorian retrospective study also found an increased risk of diabetic ketoacidosis associated with SGLT2 inhibitors (odds ratio 1.48). Hospital inpatients had a markedly increased risk of developing diabetic ketoacidosis (odds ratio 37.4).<sup>20</sup>

Diabetic ketoacidosis in patients taking SGLT2 inhibitors can present with normal or only mildly elevated glucose concentrations. This is due to the ongoing SGLT2 inhibitor-induced glycosuria. It is therefore prudent to test for ketones in any unwell patient taking an SGLT2 inhibitor regardless of their blood glucose concentration.

The Australian Diabetes Society has published recommendations based on expert opinion to try to reduce the risk of perioperative diabetic ketoacidosis.<sup>21</sup> Recommendations include withholding SGLT2 inhibitors for three days before major surgical procedures and not restarting them until the patient is eating and drinking.<sup>21</sup>

### Amputations

An approximately twofold increased risk of lower limb amputations was observed with canagliflozin in the CANVAS trial.<sup>22</sup> However, a second large randomised controlled trial of canagliflozin (CREDENCE) and a



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meta-analysis of four observational databases did not find a significantly increased risk.<sup>23,24</sup> Higher rates of lower limb amputations were not seen in the EMPA-REG OUTCOME<sup>25</sup> or DECLARE-TIMI 58 trials.<sup>17</sup>

An analysis of reports to the World Health Organization suggests an increased risk of lower limb amputations with canagliflozin, empagliflozin and dapagliflozin. However, these results may have been confounded by reporting bias.<sup>26</sup>

### Fractures

Current data are inconclusive regarding SGLT2 inhibitors and fracture risk. In one study, canagliflozin was associated with decreased bone mineral density at the hip after two years of treatment.<sup>27</sup> The CANVAS trial found an increased relative risk of fractures (hazard ratio 1.26) with canagliflozin.<sup>22</sup> However, a meta-analysis of 38 randomised controlled trials did not find an overall increased risk of fractures with SGLT2 inhibitors.<sup>28</sup> Most of these studies had follow-up periods of less than three years and further long-term studies are needed.

### Acute kidney injury

A meta-analysis of randomised controlled trials found that SGLT2 inhibitors are associated with reduced rates of acute kidney injury,<sup>29</sup> however there are numerous case reports of acute kidney injury occurring shortly after starting treatment. A transient decrease in eGFR may be seen after starting an SGLT2 inhibitor, but this does not usually progress.

### Emerging indications

Currently, SGLT2 inhibitors are not approved by the TGA for patients without type 2 diabetes, but other indications are being studied.

### Heart failure in patients without diabetes

The dapagliflozin heart failure randomised controlled trial (DAPA-HF) studied 4744 patients with heart failure and an ejection fraction less than 40%.<sup>30</sup> They were on optimal treatment for heart failure and did not have diabetes. Compared with placebo, there was a 26% relative risk reduction in worsening heart failure or cardiovascular death with dapagliflozin. There was no significant difference in adverse effects.

Ongoing studies of empagliflozin and dapagliflozin in patients with heart failure with preserved and reduced ejection fraction (EMPEROR-Reduced, EMPEROR-Preserved and DELIVER) will add to the evidence in this area.

### Type 1 diabetes

Due to their non-insulin mediated mechanism of glycaemic control, there has been interest in using SGLT2 inhibitors for patients with type 1

diabetes. There are several trials in type 1 diabetes but they are of short duration (maximum 52 weeks). A small decrease in HbA1c is seen (on average 0.2–0.45%) but at the cost of a 2–3-fold increase in diabetic ketoacidosis.<sup>31</sup>

Dapagliflozin was approved in early 2019 by the European Medicines Agency for patients with type 1 diabetes who are overweight. However, the US Food and Drug Administration voted against approving empagliflozin.

The SGLT2 inhibitors are not approved in Australia for type 1 diabetes. Any off-label use should only be considered by diabetes specialists and their patients with a clear plan to reduce the risk of diabetic ketoacidosis, for example by ketone monitoring.

### The role of SGLT2 inhibitors in practice

In type 2 diabetes there are many second-line options, both oral and injectable, which can be added to first-line metformin. The Australian Diabetes Society has published a treatment algorithm which provides guidance to practitioners.<sup>32</sup> Key points include ensuring all patients receive education regarding lifestyle measures and weight management and individualising HbA1c targets. After metformin, add-on second-line pharmacotherapy includes sulfonylureas, SGLT2 inhibitors, dipeptidyl peptidase-4 inhibitors, insulin or glucagon-like peptide-1 receptor analogues. Choosing which drug is best involves balancing the harm–benefit for the individual patient. The risk of cardiovascular and renal disease should be assessed. Patients at higher cardiovascular risk (for example a previous event or known atherosclerosis), with heart failure, or with chronic kidney disease (but stable eGFR above 45 mL/min/1.73 m<sup>2</sup>) may benefit from SGLT2 inhibitors.

### Conclusion

SGLT2 inhibitors are oral glucose-lowering drugs which cause modest weight loss and blood pressure reduction. They have low rates of hypoglycaemia, except when used in conjunction with insulin or sulfonylureas. In patients with type 2 diabetes and cardiovascular disease, SGLT2 inhibitors reduce all-cause mortality, rates of hospitalisation for heart failure and the progression of renal disease.

Adverse effects are usually mild and related to glycosuria and osmotic diuresis. Serious adverse effects are rare, but may include diabetic ketoacidosis, severe genitourinary infections and possibly lower limb amputations and fractures. ◀

*Conflict of interest: none declared*



### SELF-TEST QUESTIONS

*True or false?*

3. In a patient with normal kidney function, a transient decline in glomerular filtration after starting an SGLT2 inhibitor is an indication to stop treatment.
4. Diabetic ketoacidosis does not occur in patients with type 2 diabetes treated with an SGLT2 inhibitor.

*Answers on page 179*



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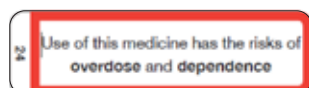
## New warning label for opioid products

*Aust Prescr* 2020;43:172  
<https://doi.org/10.18773/austprescr.2020.059>

First published  
11 August 2020

In 2018 the Therapeutic Goods Administration (TGA) released a consultation paper called *Prescription strong (Schedule 8) opioid use and misuse in Australia – options for a regulatory response*. One of the regulatory options was the addition of a warning on the packaging of opioid products identifying the risks of overdose and dependence.<sup>1,2</sup>

In collaboration with other organisations, the Pharmaceutical Society of Australia (PSA) has now developed a cautionary advisory label warning of the risk of opioid overdose and dependence. These labels are applied by pharmacists to medicines at the time of dispensing and are intended to be used as an aid to counselling patients about the safe and effective use of medicines. The label for opioids is:



As an additional counselling aid for patients, families and carers, a patient information handout has been developed. It is available in the [Australian Pharmaceutical Formulary](#). Pharmacists may provide patients with this handout at the time of dispensing.

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## New drugs

### Darolutamide

**Approved indication: prostate cancer**

**Nubeqa (Bayer)**

**300 mg film-coated tablets**

Androgen deprivation therapy (gonadotrophin-releasing hormone analogues or castration) is a key part of the medical management of prostate cancer.<sup>1</sup> It reduces tumour growth by lowering serum testosterone. Despite this treatment the cancer will eventually progress and become 'castration-resistant'. Anti-androgens such as apalutamide and enzalutamide may then be prescribed to delay metastasis. Darolutamide is an anti-androgen that acts as an antagonist at the androgen receptor.

The recommended dose of darolutamide is 600 mg twice daily with food. The drug undergoes metabolism by several enzyme systems. They include cytochrome P450 (CYP) 3A4, so inhibitors of this enzyme, such as itraconazole, will increase concentrations of darolutamide and concentrations will be decreased by enzyme inducers such as rifampicin. The half-life is approximately 20 hours with the metabolites being excreted in the urine and faeces. A reduced dose (300 mg twice daily) is recommended if the patient has severe renal impairment (eGFR 15–29 mL/min/1.73 m<sup>2</sup>) or moderate hepatic impairment.

The approval of darolutamide appears to be mainly based on one phase III double-blind, randomised trial. This was the Androgen Receptor Antagonising Agent for Metastasis-free Survival (ARAMIS) trial.<sup>2</sup> It involved 1509 men with castration-resistant prostate cancer who had a rising concentration of prostate-specific antigen, but no detectable metastases. They added darolutamide or a placebo to their androgen deprivation therapy. The 955 men in the darolutamide group remained free of metastasis for a median of 40.4 months. This compares with a metastasis-free survival of 18.4 months in the 554 who took a placebo. The median progression-free survival was 36.8 months with darolutamide and 14.8 months with placebo. Although darolutamide delayed the progression of pain (40.3 vs 25.4 months), its effect on the quality of life was similar to placebo.<sup>2</sup>

During the trial 83.6% of the darolutamide group and 76.9% of the placebo group had an adverse event. Most adverse events occurred with a

similar frequency, including death (3.9% vs 3.2%). Approximately 9% of each group withdrew from the trial because of adverse events. Fatigue was more frequent with darolutamide (12.1% vs 8.7%). Hypertension affected 6.6% of the darolutamide group. This could be a problem in practice as patients with a recent history of cardiovascular events were excluded from the ARAMIS trial.<sup>2</sup>

As anti-androgen therapy is known to delay the progression of prostate cancer, it is not surprising that darolutamide has greater efficacy than a placebo. Although there has not been a comparative trial, for patients with non-metastatic castration-resistant cancer the median metastasis-free survival appears to be similar for darolutamide, apalutamide and enzalutamide. When the results of the ARAMIS trial were published the median overall survival could not be calculated. There had been 78 deaths with darolutamide and 58 with placebo.<sup>2</sup> A preliminary report of longer term data gives the three-year survival as 83% for darolutamide and 77% for placebo.<sup>3</sup>

**T** manufacturer provided the product information

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

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

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<https://doi.org/10.18773/austprescr.2020.061>

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

## NEW DRUGS

## Obeticholic acid

*Aust Prescr* 2020;43:174–5  
<https://doi.org/10.18773/austprescr.2020.063>

**Approved indication: primary biliary cholangitis****Ocaliva (Chiesi)****5 mg and 10 mg tablets**

Primary biliary cholangitis is an autoimmune condition in which the bile ductules in the liver are destroyed. Cholestasis and inflammation cause altered liver function with raised concentrations of alkaline phosphatase. The damage leads to cirrhosis, hence the condition is also known as primary biliary cirrhosis. Treatment with ursodeoxycholic acid can slow progression and delay the need for a liver transplant. The regulation of bile acids involves the farnesoid X nuclear receptor. Activating the receptor reduces the concentrations of bile acids in the liver. This leads to reduced inflammation and fibrosis. Obeticholic acid acts as an agonist on this receptor.

After absorption obeticholic acid is conjugated with glycine or taurine and secreted into bile. The conjugates can be reabsorbed from the gut, setting up an enterohepatic recirculation. Most of the dose is eventually excreted in the faeces. If the patient has moderate or severe hepatic impairment (Child-Pugh Class B and C), the usual starting dose of 5 mg daily is reduced to 5 mg weekly. In patients taking warfarin, obeticholic acid will decrease the INR. Bile acid binding resins should not be taken within 4–6 hours of obeticholic acid.

Daily doses of 10 mg, 25 mg, 50 mg or placebo were studied in a phase II trial involving 165 patients with primary biliary cirrhosis that was not well controlled by ursodeoxycholic acid. These patients were treated for three months. The mean concentrations of alkaline phosphatase were reduced by 21–25% with obeticholic acid but only by 3% with placebo. This biochemical benefit was maintained in the 78 patients who continued treatment in a 12-month extension of the trial.<sup>1</sup> While the higher doses had similar efficacy to the 10 mg dose, they were more frequently associated with severe pruritus so they were not used in a phase III trial.

The double-blind phase III trial randomised 73 patients to take obeticholic acid 10 mg daily and 70 patients to take 5 mg for six months then increase to 10 mg according to the response and adverse effects. Another 73 patients took a placebo. If tolerated, all patients continued to take ursodeoxycholic acid. The primary end point of the study was at least a 15% reduction in alkaline phosphatase, with a concentration less than 1.67 times the upper limit of normal, and a total bilirubin concentration no higher than the upper limit of normal. After one year this composite end

point had been achieved by 47% of the 10 mg group and 46% of the 5–10 mg group. This was statistically better than the 10% response in the placebo group.<sup>2</sup>

Following the double-blind phase, 193 patients entered an extension study. They were given open-label obeticholic acid 5 mg which could be increased after three months according to the response. The proportions of patients achieving the primary end point were 53% at 24 months, 55% at 36 months and 51% at 48 months. Concentrations of alkaline phosphatase and other liver enzymes were significantly reduced.<sup>3</sup>

In the long-term extension study the most frequent adverse effect was pruritis affecting 77% of the patients. Other common adverse events included fatigue, urinary tract infection, headache and arthralgia.<sup>3</sup> There is a risk of liver-related adverse reactions. These include flare-ups of cholangitis, jaundice and ascites. The risk of these adverse events increases with the dose of obeticholic acid so 10 mg daily is the highest recommended dose. Possibly because of its action on bile acids, obeticholic acid has an effect on lipids. Concentrations of low-density lipoprotein may increase and high-density lipoprotein cholesterol may decrease.<sup>2</sup>

If primary biliary cholangitis does not respond adequately to ursodeoxycholic acid, or if the patient cannot tolerate it, obeticholic acid can be added to therapy. Most patients will then have a reduction in alkaline phosphatase concentrations, but the clinical consequences are less clear. In the double-blind phase III trial there was no difference in liver fibrosis between obeticholic acid and placebo.<sup>2</sup> The 10-year predicted risk of death or liver transplantation only reduced slightly, from 20% at baseline to 18.95% at 48 months.<sup>3</sup> As the patients in the trial had relatively early disease, it is uncertain what effect obeticholic acid will have in more advanced disease. It will take several years before it is known whether or not obeticholic acid has any clinical benefit in primary biliary cholangitis.

**T** manufacturer provided the product information

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

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



## NEW DRUGS

## Remdesivir

*Aust Prescr* 2020;43:176–7

<https://doi.org/10.18773/austprescr.2020.060>

First published  
18 August 2020

### Approved indication: COVID-19

#### Veklury (Gilead)

#### vials containing 100 mg powder or 100 mg/20 mL concentrate

Remdesivir, an antiviral originally designed to target the Ebola virus, has been provisionally approved for COVID-19. It is indicated for adults and adolescents with pneumonia who require supplemental oxygen. Remdesivir is a nucleotide analogue that delays replication of viral RNA. It comes in the form of a prodrug which is metabolised to the active form (remdesivir triphosphate) once it enters cells. In vitro studies have shown that it has antiviral activity against the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).<sup>1</sup>

There have been several studies of remdesivir in hospitalised patients with COVID-19. These have included a compassionate use program,<sup>2</sup> two placebo-controlled trials<sup>3,4</sup> and two dosing trials<sup>5,6</sup> (see Table). Apart from the placebo-controlled trial in China,<sup>4</sup> all of these studies are ongoing and results are preliminary.

The studies enrolled patients with severe disease and an oxygen saturation of 94% or less, except the unpublished dosing trial which enrolled patients with moderate disease.<sup>6</sup> All except the dosing studies included (some) patients who required mechanical ventilation. Trials assessed a 10-day intravenous course of remdesivir starting with a loading dose of 200 mg on day 1 followed by 100 mg on subsequent days. The two dosing trials compared a 10-day course with a 5-day course of remdesivir.<sup>5,6</sup>

The Adaptive COVID-19 Treatment Trial found that patients receiving remdesivir recovered faster than those receiving placebo (median of 11 days vs 15 days).<sup>3</sup> However, in the Chinese placebo-controlled trial, remdesivir was not associated with a statistically shorter time to clinical improvement compared to placebo (median 21 days vs 23 days). This trial was terminated early due to control of the outbreak, therefore its statistical power was reduced from 80% to 58%.<sup>4</sup>

The dosing trials<sup>5,6</sup> compared a 5-day course of remdesivir with a 10-day course. One of the trials reported no statistical difference in clinical benefit between the two durations. There was no placebo arm in this trial so the magnitude of the clinical benefit could not be quantified.<sup>5</sup>

The other dosing trial<sup>6</sup> included a standard of care arm as a control. Enrolled patients were hospitalised

with moderate disease (pneumonia without reduced oxygen saturation). At 11 days, clinical improvement was statistically better in patients who received the 5-day course, but not the 10-day course, compared to standard of care (see Table). These results have not yet been published in a peer-reviewed journal.

In terms of safety, increased liver enzymes are very common with remdesivir. It is therefore not recommended in people with elevated alanine aminotransferase ( $\geq 5$  times the upper limit of normal). Headache, nausea and rash were common adverse events in the trials.

Remdesivir is a category B2 drug in pregnancy. Over 300 pregnant women have received it through a compassionate use program but there are no safety data available from this so far. Animal studies show that a metabolite of remdesivir is excreted in breastmilk.

Remdesivir is administered by an intravenous infusion. Peak plasma concentrations are reached 1.5–5 hours after the start of the infusion. Most of the dose is excreted as metabolites in the urine (74%) and faeces (18%). This product contains the excipient sulfobutyl betadex sodium which is renally cleared. As this accumulates in people with impaired kidney function, remdesivir is not recommended when the estimated glomerular filtration rate is less than 30 mL/min.

Drug–drug interaction studies have not been carried out with remdesivir so the potential for interactions is not known. In vitro studies suggest that strong inhibitors and inducers of cytochrome P450 (CYP) enzymes 2C8, 2D6 and 3A4 may affect remdesivir plasma concentrations. Concomitant hydroxychloroquine or chloroquine is not recommended due to possible antagonism.

Remdesivir seemed to be marginally better than placebo or standard of care in patients with severe COVID-19 in some of the clinical trials but not others. However, clinical data are limited and most results are preliminary. More comprehensive evidence of benefit is awaited by the Therapeutic Goods Administration. At this stage, the Australian guidelines for the clinical care of people with COVID-19 give a conditional recommendation for remdesivir stating that, where possible, remdesivir should be used in the context of a clinical trial but can be considered outside of a trial setting for patients with moderate, severe and critical COVID-19. However, they do warn against its routine use in pregnant and lactating women outside of a trial.

**T T** manufacturer provided additional useful information

**Table Efficacy of the antiviral remdesivir\* for severe COVID-19**

Trial	Study arms	Efficacy	Mortality
Compassionate use program (single-arm) <sup>2</sup>	Remdesivir for 10 days (53 patients)	Clinical improvement in terms of oxygen requirement: 68% of patients improved, 15% got worse	13% after a median of 15 days of treatment
Placebo-controlled trial (Adaptive COVID-19 Treatment Trial) <sup>3</sup>	Remdesivir (538 patients) vs placebo (521 patients) for 10 days	Median time to recovery: <sup>†</sup> 11 vs 15 days (rate ratio 1.32, CI 1.12–1.55 P<0.001)	7.1% vs 11.9% at 14 days (HR 0.7, CI 0.47–1.04)
Placebo-controlled trial (in Hubei, China) <sup>†† 4</sup>	Remdesivir (158 patients) vs placebo (78 patients) for 10 days	Median time to clinical improvement: 21 vs 23 days (HR 1.23, CI 0.87–1.75)	14% vs 13% at 28 days
Open-label, randomised dosing trial <sup>‡ 5</sup>	Remdesivir for 10 days (197 patients) vs 5 days (200 patients)	Clinical improvement of 2 points on a 7-point scale: <sup>§</sup> 54% vs 65% Median time to recovery: 11 vs 10 days	11% (10 days) vs 8% (5 days)
Open-label, randomised dosing trial with standard of care arm <sup># 6</sup>	Remdesivir for 10 days (193 patients) vs 5 days (191 patients) vs standard of care (200 patients)	Clinical improvement on a 7-point scale <sup>§</sup> compared to standard of care at day 11: • 5-day course – OR 1.65 (CI 1.09–2.48, p=0.17) • 10-day course – OR 1.31 (CI 0.88–1.95, p=0.18)	1% (10 days) vs 0% (5 days) vs 2% (standard of care)

CI confidence intervals, HR hazard ratio, OR odds ratio

\* Patients received a loading dose of 200 mg on day 1 followed by 100 mg a day after that.

† Recovery defined as hospital discharge or hospitalisation for infection control purposes only.

†† Concomitant treatments for COVID-19 were allowed including lopinavir/ritonavir, interferons and corticosteroids.

‡ Patients receiving mechanical ventilation were not included in this trial.

§ 1=death, 2=hospitalised and receiving invasive ventilation, 3=hospitalised receiving non-invasive ventilation or high-flow oxygen, 4=hospitalised receiving low-flow oxygen, 5=hospitalised with no oxygen requirement but needing medical care, 6=hospitalised with no oxygen or medical care needed, 7=not hospitalised

# Patients had moderate disease (pneumonia without reduced oxygen saturation).

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

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

## NEW DRUGS

Aust Prescr 2020;43:178–9

<https://doi.org/10.18773/austprescr.2020.053>First published  
6 August 2020

## Upadacitinib

## Approved indication: rheumatoid arthritis

## Rinvoq (AbbVie)

## 15 mg modified-release tablets

Upadacitinib is the third Janus kinase (JAK) inhibitor to be approved for rheumatoid arthritis after baricitinib and tofacitinib. These drugs modify immune and inflammatory processes by blocking the cytokine pathway that leads to the activation of lymphocytes.<sup>1,2</sup>

Upadacitinib is indicated for patients with moderate–severe rheumatoid arthritis who have not adequately responded, or are intolerant, to at least one or more conventional disease-modifying antirheumatic drugs (DMARDs). The drug has been investigated in several phase III randomised clinical trials.<sup>3–7</sup> Response to treatment was defined as at least a 20% improvement on the American College of Rheumatology scale (ACR20). At the recommended daily dose of 15 mg, statistically more people responded to upadacitinib, as monotherapy or when added to conventional DMARDs, than to placebo or methotrexate (see Table). The most common adverse effects with upadacitinib in the trials included urinary and upper respiratory

tract infections, altered liver function and nausea. Rare but serious adverse events included malignancy, thrombosis and gastrointestinal perforation.

As with other JAK inhibitors, serious and sometimes fatal infections can occur with upadacitinib – pneumonia and cellulitis were the most commonly reported in the trials. Opportunistic infections such as tuberculosis, multi-dermatomal herpes zoster, oral candidiasis, cryptococcosis and pneumocystosis have also occurred. Upadacitinib should not be used in patients with active infections and caution is urged in those with chronic or recurrent infection or a history of tuberculosis. Care should also be taken in older patients and those with diabetes. Screening for tuberculosis and viral hepatitis is recommended and vaccinations, particularly against herpes zoster, should be up to date before treatment is started.

Upadacitinib can be prescribed as monotherapy or in addition to methotrexate and other conventional DMARDs. It should not be given with other JAK inhibitors, biological DMARDs or potent immunosuppressants like azathioprine or ciclosporin. Upadacitinib should not be started if lymphocytes are less than  $0.5 \times 10^9$  cells/L or neutrophils are less than  $1 \times 10^9$  cells/L. Haemoglobin must be at least

Table Efficacy of upadacitinib in moderate–severe rheumatoid arthritis

Trial	Treatment	Efficacy - ACR20*
SELECT EARLY <sup>3</sup> 947 methotrexate-naïve patients randomised to upadacitinib or methotrexate for 12 weeks	upadacitinib 15 mg/day	76%
	upadacitinib 30 mg/day	77%
	methotrexate	54%
SELECT MONOTHERAPY <sup>4</sup> 648 patients with inadequate response to methotrexate randomised to switch to upadacitinib monotherapy or continue methotrexate for 14 weeks	upadacitinib 15 mg/day	68%
	upadacitinib 30 mg/day	71%
	methotrexate	41%
SELECT NEXT <sup>5</sup> 661 patients with inadequate response to at least one conventional DMARD (methotrexate, sulfazine or leflunomide) randomised to add upadacitinib or placebo for 12 weeks	upadacitinib 15 mg/day	64%
	upadacitinib 30 mg/day	66%
	placebo	36%
SELECT COMPARE <sup>6</sup> 1629 patients with inadequate response to methotrexate randomised to add upadacitinib, adalimumab or placebo for 48 weeks (ACR20 measured at 12 weeks)	upadacitinib 15 mg/day	71%
	adalimumab 40 mg every 2 weeks	63%
	placebo	36%
SELECT BEYOND <sup>7</sup> 499 patients with inadequate response or intolerance to biological DMARDs and receiving conventional DMARDs randomised to add upadacitinib or placebo for 12 weeks	upadacitinib 15 mg/day	65%
	upadacitinib 30 mg/day	56%
	placebo	28%

DMARD disease-modifying antirheumatic drug

\* defined as the proportion of patients who had at least a 20% improvement on the American College of Rheumatology scale

80 g/L. Upadacitinib is not recommended in severe hepatic impairment (Child-Pugh C).

Upadacitinib is mainly metabolised by cytochrome P450 (CYP) 3A4, and to a lesser extent by CYP2D6. It has no active metabolites. Steady-state concentrations are reached within four days following once-daily dosing. It has a half-life of 9–14 hours. Two-thirds of the dose is excreted unchanged in the urine (24%) and faeces (38%) and a third is excreted as metabolites.

Giving upadacitinib with a strong CYP3A4 inducer (e.g. rifampicin) may decrease its efficacy, while strong CYP3A4 inhibitors (e.g. clarithromycin) could increase the risk of toxicity. Patients should therefore be closely monitored if they are taking these types of medicines.

Upadacitinib is a category D drug and is not recommended in pregnancy. In animal studies, it caused fetal malformations in early pregnancy. The drug is also not recommended during breastfeeding and was found to be excreted in the milk of lactating rats.

Upadacitinib seems to be effective in moderate–severe rheumatoid arthritis used alone or added to a patient's conventional DMARD therapy. However, close monitoring is recommended as there is a risk of serious and sometimes fatal adverse effects, particularly infections. To date, there have been no head-to-head trials with other JAK inhibitors.

**T** manufacturer provided the product information

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## ANSWERS TO SELF-TEST QUESTIONS

- |         |         |
|---------|---------|
| 1 False | 2 False |
| 3 False | 4 False |

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