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Faecal microbiota transplantation: indications, evidence and safety

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SUMMARY

The human gut contains many species of microorganisms, many of which have a role in maintaining good health. The gut microbiota can be affected by diet, diseases and drugs, especially antibiotics.

Faecal microbiota transplantation involves transplanting faecal material from a healthy person to a patient, with the aim of treating disease. It is a recommended treatment option for patients with recurrent or refractory *Clostridioides difficile* as it has a cure rate over 90%.

There is evidence that faecal microbiota transplantation can induce remission in ulcerative colitis, however maintenance of remission data are lacking. For other diseases it currently should not be used outside a clinical trial.

Stool donors have to be healthy and are screened for a range of diseases. As faecal material is usually transplanted during colonoscopy, the recipient must have bowel preparation before the procedure.

Adverse effects are mainly gastrointestinal and usually resolve in the week following transplantation. There are limited data on long-term safety.

Introduction

Faecal microbiota transplantation is the transfer of faecal material from a healthy individual to another person with the aim of treating a disease. It can be described as 'the ultimate probiotic' as it donates a much greater number and diversity of bacterial strains than any available probiotic.

The deliberate transfer of faecal material between individuals has a long history. It was first reported as a therapy in 4th century China. A human faecal suspension was given by mouth to treat patients with severe diarrhoea.[1] In North Africa camel faeces have been used as a treatment for dysentery.[2] Human faecal microbiota transplantation was first described in the western literature in 1958 for the treatment of four critically ill patients with pseudomembranous colitis.[3] The precise mechanisms by which faecal microbiota transplantation treats disease are not fully understood.

Gut microbiome

The organisms living in the gut are termed the gut microbiota, while the gut microbiome consists of the genetic material of these organisms. The human gastrointestinal microbiota contains approximately 3.9×10^{13} organisms, a figure similar to the number of human cells in the body.[4] It consists of bacteria, fungi, protozoa, archaea and viruses (including phage viruses that infect bacteria). The gut microbiota is dominated by two main phyla of bacteria – Firmicutes and Bacteroidetes. These make up 90%, with eight other phyla making up the remaining 10%.[5]

Many of the microorganisms in the gut have co-evolved with humans and perform essential functions, such as the production of important metabolic products. For example, bacteria metabolise resistant starch in the colon to produce butyrate, a short chain fatty acid which is the primary and essential energy source of enteric colonocytes.[6] Some intestinal microbiota live in close association with the colonic epithelium and play a role in regulating local and distant immune function.[7] Others regulate intestinal barrier functions, or protect against pathogens such as vancomycin-resistant enterococci by competitive inhibition.[8]

Dysbiosis

The gut microbiota is mostly acquired during the first 3–4 years of infancy, with mode of delivery, breastfeeding, diet and the local environment all playing a role.[9,10] Beyond this time the adult gut microbiome remains relatively stable. It can be altered by persistent dietary or lifestyle changes, disease, travel, drugs or surgery.[11]

The use of systemic antibiotics is the most well-studied risk factor for altering the gut microbiota. It results in a decreased diversity of species, loss of antimicrobial peptides produced by commensal bacteria, and loss of resistance to colonisation because the competitive inhibition of pathogens is reduced.[12]

Perturbation of the gut microbiota associated with disease is termed dysbiosis. This has been associated with multiple diseases including *Clostridioides difficile* infection, colonisation with drug-resistant bacteria, inflammatory bowel disease, irritable bowel syndrome and metabolic syndrome.[13] These associations with dysbiosis have prompted research into possible aetiological roles that the microbiota may have and whether modification of the microbiota will have a therapeutic effect in these diseases.

Indications

At present, faecal microbiota transplantation is predominantly used for the treatment of *C. difficile*. First-line treatment for mild *C. difficile* is oral metronidazole and, for more severe infection or recurrent episodes, vancomycin is recommended.[14] Patients who have had two or more recurrences of *C. difficile* despite recommended antibiotic therapy have a low chance of responding to further antibiotic therapy. Transplantation offers a better chance of cure and its efficacy is supported by evidence from multiple randomised controlled trials.[13,14] A single faecal transplant cures 80–90% of *C. difficile* cases, compared to cure rates of 26–30% with vancomycin, and repeated transplantation increases cure rates to more than 95%.[15] Evidence also supports the use of transplantation following severe *C. difficile* infection which has resulted in shock or supportive care, as well as in cases of disease refractory to antibiotic therapy.[14,16-18] Faecal microbiota transplantation reduces cost and at the same time improves quality of life compared with vancomycin, saving over A$4,000 per patient treated.[19] It is thus a recommended therapy for recurrent, refractory or severe *C. difficile* in national and international guidelines.[14,16]

There is evidence that faecal microbiota transplantation induces remission of active ulcerative colitis.[17,18,20] However, more data are required before it can be recommended as maintenance therapy in ulcerative colitis.[21]

Donor screening protocol

Preferred stool donors are healthy people without pre-existing disease or risk factors for disease. These individuals are recruited by stool banks and undergo a thorough screening process that includes a questionnaire to exclude those with disease, exposure to transmissible diseases, or behavioural risk factors for transmissible diseases. Disease exclusions include, but are not limited to, blood- or stool-borne infections, gastrointestinal disorders, malignancy, atopy, metabolic syndrome and autoimmune diseases. People who have recently taken antibiotics or have travelled to areas with a high risk of traveller's diarrhoea are excluded. BMI is then calculated and those who are obese or underweight are excluded.

Donors who pass the screening questionnaire and BMI measure then undergo extensive blood and stool tests for transmissible diseases. This includes checking for blood- and stool-borne infections and multidrug resistant organisms in the stool.

Preparation and delivery

Currently there is no universal protocol for preparing a patient for faecal microbiota transplantation. Stool is usually mixed with saline or water with between 12.5% and 25% stool in the suspension by weight. The transplant can be fresh or thawed frozen stool as these are equally effective.[22] When freezing stools 10% glycerol is often added to preserve bacterial viability.[23]

Patients preparing to receive a faecal microbiota transplantation for *C. difficile* are required to take vancomycin for 5–10 days and then stop 24–36 hours before the procedure. For colonoscopic delivery, patients undergo bowel preparation approximately 12 hours before the procedure. On the day it is common for the patient to be given loperamide to assist with retaining the transplanted material.[24]

The methods of delivery are via the upper gastrointestinal route (nasoduodenal, oral capsules), or lower gastrointestinal route (colonoscopic delivery into the ascending colon, or retention enemas). However, colonoscopic delivery is the most common method. It has the most evidence in the literature, with high rates of cure across studies.[25] Nasogastric and nasoduodenal delivery tend to have higher rates of minor adverse effects relative to other methods.[15]

Safety

Faecal microbiota transplantation for recurrent *C. difficile* has a good short-term safety record. There are very few adverse effects directly attributed to the procedure. Most reported adverse events have been self-limiting gastrointestinal symptoms including abdominal cramps, diarrhoea and constipation, which resolved within one week.[25] There have been at least two deaths from aspiration pneumonia related to sedation given at the time of faecal microbiota transplantation. There has been at least one death from transmission of a multidrug resistant *Escherichia coli* organism, however the donor in this case had not been tested for this organism.[26] These deaths are relatively small in number compared to the large number of transplantations performed (at least 50,000 in the USA since 2013).[27]

The long-term safety of faecal microbiota transplantation is not yet well established. Most of the studies have only been reported in the last decade and there have been no registries until recently.

Emerging indications

A large number of diseases have been associated with gut dysbiosis and the success of faecal microbiota transplantation in treating recurrent *C. difficile* has encouraged research into transplantation as a potential therapy for these diseases. There have been trials in irritable bowel syndrome,[28-30] hepatic encephalopathy,[31] Crohn's disease,[32] primary sclerosing cholangitis[33] and autism.[34] However, the evidence for the efficacy and safety of faecal microbiota transplantation for these conditions is currently limited and further studies are warranted before it can be recommended as therapy outside of clinical trials. While trials have the possibility of broadening the indications for transplantation, they could also guide the development of microbial therapeutics that may replace or complement faecal microbiota transplantation in the future.

Conclusion

Faecal microbiota transplantation is an effective treatment option for recurrent infection with *C. difficile*. Its use in other indications at present should be part of a clinical trial. ◄

Conflict of interest: none declared

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Management of dental pain in primary care

SUMMARY

Patients sometimes present to a medical practitioner with dental pain if they cannot see a dentist.

Doctors need to be aware of the common dental diseases that result in pain so they can help to manage the patient's symptoms until they are able to see a dentist.

Appropriate advice regarding analgesics for dental pain is important. Paracetamol and ibuprofen are more effective in combination than either of them alone, with or without opioids.

Antibiotics are only indicated as an adjunct to dental treatment when there are signs of systemic involvement, progressive and rapid spread of infection, or when the patient is immunocompromised.

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Introduction

Patients may present to a medical practitioner with dental pain, dento-maxillofacial trauma and treatment-related complications. This happens frequently in emergency departments, but also in general practice.[1] A recent survey found that dental conditions accounted for over 70,000 avoidable hospital admissions in Australia during 2016–17.[2] Yet, many doctors have limited training in the diagnosis and management of common dental problems.[3]

Besides referral to a dentist, the medical practitioner can provide appropriate advice regarding analgesics, with consideration of the patient's medical history (including recent dental treatment), the benefits and risks of the drugs and severity of the pain. It is also important to know when antibiotics should and should not be prescribed.[4] Community pharmacists also see many patients with dental pain, particularly out of hours, and need guidance about what to advise.

Questions to ask when assessing oral pain

When obtaining a pain history, the mnemonic SOCRATES can be useful:[5]

Site – Where is the pain?

Onset – When did it start?

Character – Can you describe the pain?

Radiation – Does the pain spread anywhere?

Associations – Are there other problems associated with the pain?

Time course – Does the pain follow any pattern? How long does it last?

Exacerbating or relieving factors – Does anything worsen or improve it?

Severity – How bad is the pain?

Common types of dental pain

Dental pain is usually acute, unilateral and localised within the mouth.[6] It can be exacerbated by thermal or osmotic stimuli or when biting and can present with swelling. Figure 1 indicates where some of the more common conditions that cause dental pain can occur in a tooth.[7]

Pain exacerbated by thermal or osmotic stimuli

The management of dental pain that worsens with thermal or osmotic stimuli (e.g. sweets or acids) is outlined in Fig. 2. If the patient reports sensitivity or sharp, shooting pain to cold, hot or osmotic stimuli lasting only seconds to minutes, the painful tooth is likely to have an inflamed pulp. This should resolve and is called reversible pulpitis. If the inflammation progresses, the pulp may not be able to heal. This results in irreversible pulpitis. In this case, the patient may report dull or throbbing, poorly localised pain of longer duration.[8]

The term dentinal hypersensitivity is used interchangeably with reversible pulpitis as the patient presents with the same symptoms. However, dentinal hypersensitivity is related to exposed dentine.

Occasionally, temporomandibular disorders can arise secondary to pulpitis. This can present as odontogenic and non-odontogenic pain simultaneously.[9] There is a lack of evidence for the use of antibiotics to reduce pain associated with irreversible pulpitis and the patient should be advised to seek prompt dental treatment.[10]
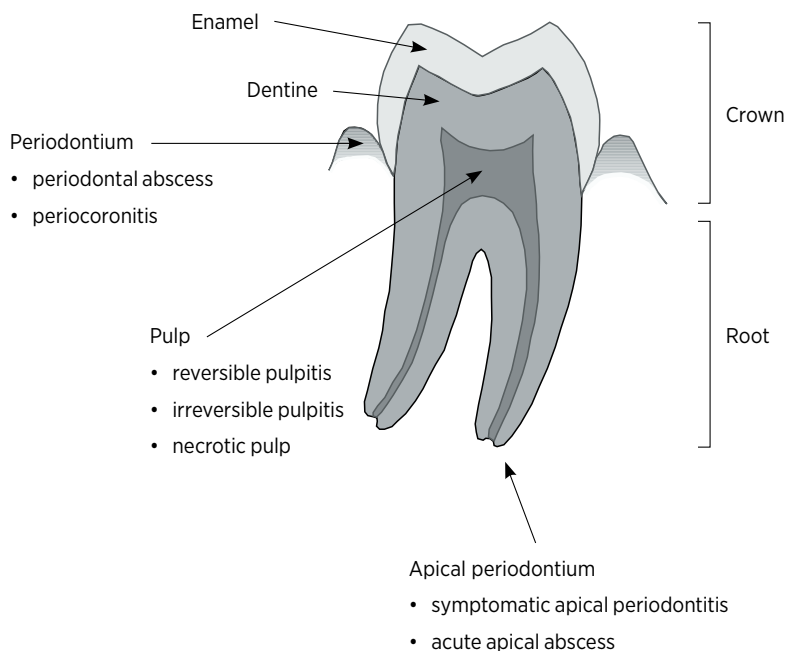
Pain when biting

The management of dental pain from biting is outlined in Fig. 3. When assessing the patient, consider the character and location of the pain. Sharp pain with short duration may be localised to a vital tooth with cracks or dislodged dental restorations.[11]

Fig. 1 **Diagram showing where common painful conditions occur in a molar tooth**

When pulp inflammation progresses to pulp necrosis, the symptoms associated with thermal or osmotic stimuli may resolve initially. Dull throbbing pain localised to a tooth with an infected root canal system can then occur when there is inflamed periodontium around the root apex (symptomatic apical peridontitis). Knowing the patient's history of symptoms and past dental treatment can be useful as pulp inflammation and necrosis usually develop from tooth decay. A patient with a history of root canal therapy can develop symptoms over time if the root canal system remains or becomes re-infected.

Other causes of dull throbbing pain include:

- food impaction – together with bacterial plaque this can result in gingival inflammation[7]
- bruxism (grinding of teeth)
- temporomandibular disorders
- oral ulceration
- periodontal issues with wisdom teeth (pericoronitis) – this may present with continuous pain localised near a wisdom tooth which is exacerbated by eating or brushing
- acute necrotising ulcerative gingivitis – this results from non-contagious infection of the gums and may present with painful bleeding, ulcerative gingival tissues and halitosis[12]

- dry socket (alveolar osteitis) – this may present with pain 1–4 days after tooth extraction so patients should be asked about recent dental treatment. The pain may radiate to the ear, eye or temporal region and be accompanied by halitosis or an unpleasant taste.[6]

When pain occurs with a temporal pattern (e.g. intermittent pain), it is likely to a have a non-odontogenic cause and the clinician should consider myalgia related to bruxism, cluster headaches or neuropathic pain.[13] A patient with nocturnal bruxism may report discomfort, fatigue or pain in the jaw muscles and headache, especially in the morning.[14]

Pain with swelling

Urgent referral to a dentist is indicated when there is dental pain with swelling. A patient with an acute apical abscess will experience a rapid onset of spontaneous pain, which can sometimes be poorly localised and present with firm or fluctuating swelling in the overlying soft tissues. The tooth is extremely tender when palpated or tapped.[15]

The symptoms and clinical presentation of a periodontal abscess can be confused with an acute apical abscess. However, pain from a periodontal abscess is usually localised. From the history, the patient may have had previous periodontal treatment, a history of periodontal abscess or a recent soft tissue trauma sustained during eating. On examination, there may be an ovoid swelling in the gingival tissues along the lateral surface of the root.[16] Suppuration can present spontaneously or when the abscess is pressed.[16] Again, systemic antibiotics are only indicated as an adjunctive treatment when there is systemic involvement or spread of infection, or if adequate drainage cannot be provided.[16]

Maxillary sinusitis

The symptoms associated with maxillary sinusitis can mimic pain of pulpal origin and vice versa.[17] The medical history of a patient with sinusitis may reveal recent upper respiratory tract infection, a history of chronic rhinitis or pain associated with air travel.[18] Symptoms can be unilateral or bilateral and are described as a continuous dull pain exacerbated by biting, touch, postural changes or exercise.[19] The patient may also have nasal congestion and discharge, headache, facial pain or fullness, erythema over the cheeks and olfactory disturbance.[19]

Maxillary sinusitis may be suspected to have an odontogenic cause when it does not respond to medical therapy and presents with unilateral symptoms and a history of dental or jaw pain. The patient may have a history of dental caries, periodontal disease or complications with surgery

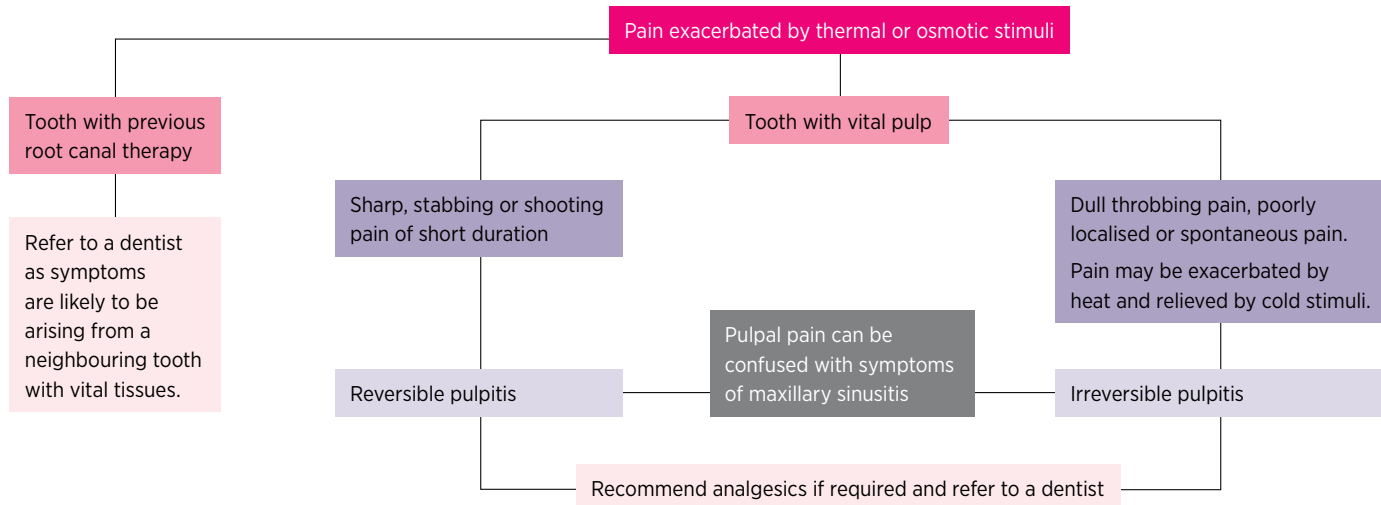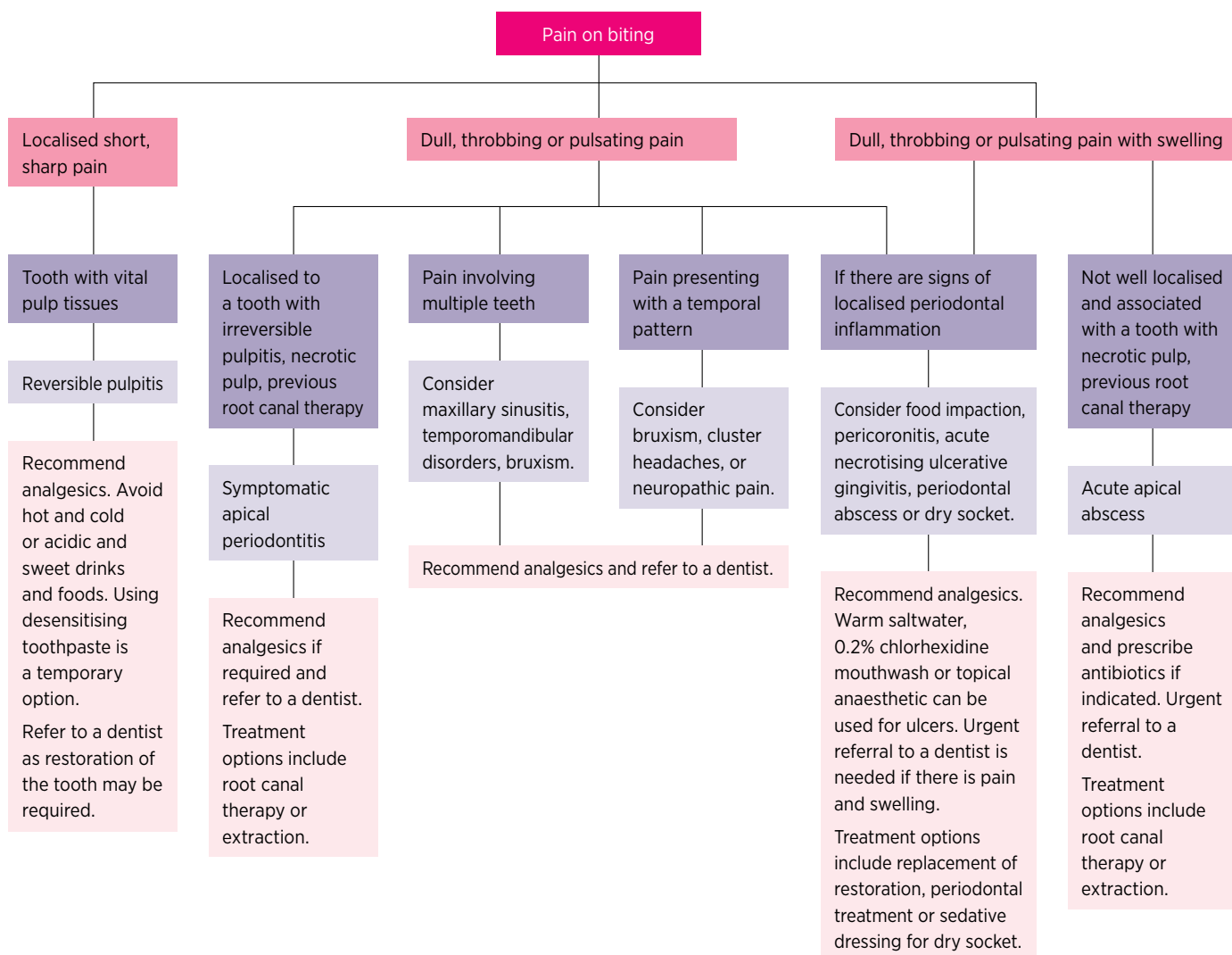*Fig.2* **Management of dental pain exacerbated by thermal or osmotic stimuli**

Pain exacerbated by thermal or osmotic stimuli

Tooth with previous root canal therapy

Refer to a dentist as symptoms are likely to be arising from a neighbouring tooth with vital tissues.

Tooth with vital pulp

Sharp, stabbing or shooting pain of short duration

Dull throbbing pain, poorly localised or spontaneous pain.
Pain may be exacerbated by heat and relieved by cold stimuli.

Reversible pulpitis

Pulpal pain can be confused with symptoms of maxillary sinusitis

Irreversible pulpitis

Recommend analgesics if required and refer to a dentist

Fig. 3 **Management of dental pain on biting**

Pain on biting

Localised short, sharp pain

Dull, throbbing or pulsating pain

Dull, throbbing or pulsating pain with swelling

Tooth with vital pulp tissues

Localised to a tooth with irreversible pulpitis, necrotic pulp, previous root canal therapy

Pain involving multiple teeth

Pain presenting with a temporal pattern

If there are signs of localised periodontal inflammation

Not well localised and associated with a tooth with necrotic pulp, previous root canal therapy

Reversible pulpitis

Consider maxillary sinusitis, temporomandibular disorders, bruxism.

Consider bruxism, cluster headaches, or neuropathic pain.

Consider food impaction, pericoronitis, acute necrotising ulcerative gingivitis, periodontal abscess or dry socket.

Acute apical abscess

Recommend analgesics. Avoid hot and cold or acidic and sweet drinks and foods. Using desensitising toothpaste is a temporary option.

Refer to a dentist as restoration of the tooth may be required.

Symptomatic apical periodontitis

Recommend analgesics and refer to a dentist.

Recommend analgesics if required and refer to a dentist.

Treatment options include root canal therapy or extraction.

Recommend analgesics. Warm saltwater, 0.2% chlorhexidine mouthwash or topical anaesthetic can be used for ulcers. Urgent referral to a dentist is needed if there is pain and swelling.

Treatment options include replacement of restoration, periodontal treatment or sedative dressing for dry socket.

Recommend analgesics and prescribe antibiotics if indicated. Urgent referral to a dentist.

Treatment options include root canal therapy or extraction.

in the posterior maxilla.[20] If sinusitis of odontogenic cause is suspected, the patient should be directed to a dentist.

Orofacial pain of non-odontogenic origin

Warning signs that can alert the clinician to pain of non-odontogenic origin are listed in the Box.[21-24] Knowing the location and timing of the pain can help to differentiate between musculoskeletal, neuropathic, vascular, primary headache or mixed conditions.[6]

Chronic orofacial pain has a non-odontogenic origin and is characterised by painful regional syndromes with a chronic unremitting pattern.[25] The most common example is temporomandibular disorders which can present as unilateral or bilateral, continuous or episodic pain.[21] The patient may complain of pain in the jaw, temple, inside or in front of the ear, which is modified by jaw movements.[22] Fibromyalgia, back pain, chronic fatigue syndrome, depression and headache can be associated with a temporomandibular disorder.[23] Clicking, crepitus, pain, trismus or locking of the temporomandibular joints can present with disruption of the disc movement.[21] Jaw claudication can potentially be a sign of temporal arteritis and the patient can be referred to an oral maxillofacial surgeon for diagnosis and management.

Analgesia

As non-steroidal anti-inflammatory drugs (NSAIDs) produce analgesic and anti-inflammatory actions by inhibiting cyclooxygenase enzymes, they are the drug of choice for dental pain. Their efficacy has been well supported by systematic reviews.[26] Taking ibuprofen

and paracetamol together has been recommended because the combination is more effective than either drug alone.[27] If NSAIDs are contraindicated, paracetamol or the combination of paracetamol and oxycodone can be recommended. As opioids result in less analgesia and more adverse effects,[27] they are only prescribed, as an adjunct to ibuprofen or paracetamol, at the lowest possible dose and shortest duration.

Administration of a dental block may be effective for initial management of severe pain before follow-up with oral analgesics, especially in an emergency department.

Topical local anaesthetics (e.g. 2% lignocaine gel) are effective for temporary pain relief in patients presenting with oral ulceration or painful oral mucosal conditions. However, the patient should be warned about the risk of further trauma when the oral mucosa is numb.[28]

Indications for antibiotic therapy

Antibiotics are only indicated as an adjunct to definitive treatment when there are systemic signs of infection (fever, malaise, lymphadenopathy, trismus), progressive and rapid spread of infection (cellulitis or Ludwig's angina) or when the patient is immunocompromised.[29] Antibiotics for odontogenic infections include:

- phenoxymethylpenicillin or amoxicillin
- amoxicillin with metronidazole
- amoxicillin with clavulanate or clindamycin.[29]

If the patient presents with spreading dental infection, systemic sepsis or the risk of airway compromise, they will need immediate referral to the emergency department.

Currently, prophylactic antibiotics are only indicated before dental procedures associated with a high risk of bacteraemia such as surgical procedures including extraction for patients with specific conditions such as prosthetic heart valves, previous infective endocarditis, some congenital heart defects, cardiac transplants with subsequent valvopathy and rheumatic fever with high risk of endocarditis.[30]

Conclusion

Management of dental pain in a medical setting follows specific guidelines for either definitive treatment or to provide relief before referral for dental treatment. Antibiotics are rarely indicated for management of odontogenic infections and are used as adjuncts to dental treatment. ◄

Conflict of interest: none declared

Box   **Some features of non-odontogenic dental pain**

- Bilateral pain or multiple teeth with pain
- Pain that does not follow a neurological distribution
- Pain described with unusual characteristics such as burning, stinging, electric, shooting, pins and needles
- Pain that is chronic and unresponsive to dental treatment
- Pain not consistently relieved by local anaesthesia
- Pain concurrent with a headache
- Pain triggered or exacerbated by palpation of trigger points or muscles of the head and neck
- Pain associated with clicking or locking of the temporomandibular joints
- Pain triggered by emotional stress, physical exercise or head position
- Pain accompanied by psychiatric features such as hallucination or delusions
- Pain associated with abnormal involuntary movements

Source: references 21-24

Glossary of dental terms

- **Acute apical abscess** – an inflammatory reaction to pulpal infection and necrosis characterised by rapid onset, spontaneous pain, tenderness of the tooth to pressure, pus formation and swelling of associated tissues.

- **Acute necrotising ulcerative gingivitis** – an inflammatory disease of the gingiva indicating an impaired host response. Signs and symptoms include pain, interdental papillary necrosis, presence of a pseudomembrane and a tendency towards spontaneous bleeding.

- **Alveolar osteitis** – localised inflammation of bone in the alveolus following tooth extraction. Also known as dry socket.

- **Bruxism** – involuntary, habitual grinding of teeth, typically during sleep.

- **Irreversible pulpitis** – a clinical diagnosis based on subjective and objective findings indicating that the inflamed dental pulp is unable to heal.

- **Pericoronitis** – acute inflammation of the gingiva or mucosa surrounding a partially erupted tooth, especially wisdom teeth.

- **Periodontium** – the tissues that support the teeth including the gingiva, alveolar mucosa, cementum, periodontal ligament and supporting alveolar bone.

- **Pulp** – a richly vascularised and innervated connective tissue of mesenchymal origin in the central space (root canal system) of a tooth.

- **Reversible pulpitis** – a clinical diagnosis based on subjective and objective findings indicating that inflammation should resolve, and the pulp will return to normal.

- **Symptomatic apical periodontitis** – inflammation and destruction of the apical periodontium causing pain on biting or when touched or tapped.

- **Temporomandibular disorders** – a group of disorders involving the masticatory muscles, the temporomandibular joint and associated structures. It can be divided into four main categories of myalgia, arthralgia, intra-articular disorders and headaches.

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Oral or intravenous antibiotics?

SUMMARY

Intravenous antibiotics are overused in hospitals. Many infections can be managed with oral antibiotics.

Oral antibiotics avoid the adverse effects of intravenous administration. They are also usually less expensive.

When intravenous antibiotics are indicated, it may be possible to switch to oral therapy after a short course. There are guidelines to aid the clinician with the timing of the switch so that there is no loss of efficacy.

Infections that may be suitable for a short course of intravenous antibiotic include pneumonia, complicated urinary tract infections, certain intra-abdominal infections, Gram-negative bacteraemia, acute exacerbations of chronic lung disease, and skin and soft tissue infections.

Bone and joint infections and infective endocarditis are managed with prolonged courses of intravenous antibiotics. However, there is research looking at the feasibility of an earlier switch to oral antibiotics in these conditions.

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Introduction

Selecting the most appropriate route of administration is part of the quality use of medicines. For many patients with bacterial infections who require treatment with an antibiotic, an oral formulation is the most appropriate choice. However, patients in hospital are often given intravenous antibiotics. While there are clinical circumstances when parenteral administration is indicated, for some infections oral therapy can be equally efficacious.

Intravenous antibiotics

Intravenous therapy is recommended, at least initially, for severe life-threatening infections and deep-seated infections because of concerns about not achieving adequate antibiotic concentrations at the site of infection. Patients who are unable to absorb or take oral drugs, for example because of vomiting, will require parenteral therapy. This route is also recommended in immunocompromised patients due to their reduced ability to fight infection.

The volume of community and hospital-based antibiotic use in Australia is higher than in comparator countries.[1] In 2017, almost one-third (32.7%) of the 21,034 prescriptions, for both oral and intravenous antibiotics, that were assessable for the voluntary hospital-based National Antimicrobial Prescribing Survey (NAPS) did not comply with either eTG Antibiotic or local guidelines.[2] A prospective study of all intravenous antibiotic use in a university-affiliated hospital found that one-third of almost 2000 days of antibiotic therapy was unnecessary.[3]

Using oral rather than parenteral antibiotics

Major advantages of oral over the intravenous route are the absence of cannula-related infections or thrombophlebitis, a lower drug cost, and a reduction in hidden costs such as the need for a health professional and equipment to administer intravenous antibiotics. Oral therapy may potentially enable an early discharge from the hospital[4,5] or directly from the emergency department.[6] For example, a single dose of intravenous antibiotic for paediatric uncomplicated urinary tract infections did not reduce the rate of representation or readmission. This suggests most children with a urinary tract infection can be managed with oral antibiotics alone.[7]

A key consideration is the bioavailability of oral antibiotics. This varies in comparison to intravenous formulations (Tables 1 and 2). Some oral antibiotics have equivalent bioavailability to the intravenous drug. They could be substituted, depending on the condition being treated and the required site of drug penetration.

In a small prospective trial, patients with moderately severe cellulitis were randomised to receive either oral cefalexin monohydrate or parenteral cefazolin. Parenteral administration was changed to oral once the cellulitis had stopped progressing and the patient was afebrile. There was no statistically significant

Table 1   **Intravenous to oral conversion for antibiotics with over 90% bioavailability**

Intravenous antibiotic	Oral antibiotic option	Oral formulations
Lincomycin or clindamycin	Clindamycin	Suspension (poor palatability) and capsules
Fluconazole	Fluconazole	Suspension and capsules
Metronidazole	Metronidazole	Suspension and capsules
Sulfamethoxazole/ trimethoprim	Sulfamethoxazole/ trimethoprim	Suspension and tablets
Doxycline	Doxycline	Tablets and capsules

Table 2   **Intravenous to oral conversion for antibiotics with 50–90% bioavailability**

Intravenous antibiotic	Oral antibiotic option	Oral formulations
Ampicillin or amoxicillin	Amoxicillin	Suspension and capsules
Benzylpenicillin	Amoxicillin	Suspension and capsules
Azithromycin	Azithromycin	Suspension and tablets
Amoxicillin/clavulanate	Amoxicillin/clavulanate	Suspension and tablets
Flucloxacillin	Flucloxacillin	Suspension (poor palatability) and capsules
	OR	
	Cefalexin	Suspension and capsules
Cefazolin	Cefalexin	Suspension and capsules
Ciprofloxacin	Ciprofloxacin	Tablets

difference in outcome between the two groups, however there were only approximately 20 patients in each arm of the trial.[8] Larger studies are required to support this result.

Shorter intravenous courses

Research is investigating whether infections that have traditionally been treated with a prolonged course of intravenous antibiotics can be managed with a shorter course of intravenous therapy. A multicentre randomised controlled trial of intra-abdominal infections, that had adequate control of the source of the infection, studied a composite outcome of surgical-site infection, recurrent intra-abdominal infection or death at 30 days. This outcome was similar in patients who only received 3–5 days of intravenous antibiotic therapy and patients who received longer courses based on cessation after resolution of physiological abnormalities.[9] This suggests that after adequate control of the source of

infection the benefits of intravenous antibiotics are limited to the first few days of treatment. However, it is important to note that there were not many patients who were immunocompromised in this study.

Randomised controlled trials have looked at other infections and length of therapy. Short-course therapy may be just as effective as longer courses[10] for:

- community-acquired or ventilator-associated pneumonia
- complicated urinary tract infections
- complicated intra-abdominal infections
- Gram-negative bacteraemia
- acute exacerbations of chronic lung disease
- skin and soft tissue infections.

Switching from intravenous to oral therapy

To develop guidelines, there was a study of switching to oral therapy after 48–72 hours of intravenous therapy. The main bacterial infections studied were respiratory tract infections, urinary tract infections, cholangitis, abdominal abscess and erysipelas. In the six weeks after completing the antibiotic course there was no recurrence of infection or readmissions due to reinfections. It was estimated that switching therapy avoided more than 6000 doses of intravenous antibiotics.[11]

A retrospective study of skin infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) evaluated the treatment of hospitalised patients across 12 European countries. It estimated that more than one-third of the patients could have been changed from intravenous antibiotics to oral therapy earlier than occurred in practice.[12]

In a single tertiary hospital a printed checklist was placed in patients' charts to encourage appropriate switching from intravenous to oral antibiotics at day three of treatment. The conditions predominantly studied were lower respiratory tract infections, urinary tract infections and intra-abdominal infections. Of the patients who were suitable for switching to oral antibiotics 61.4% were switched in response to the checklist. They had no increase in complications.[13]

There has been a systematic review of the evidence for the minimum intravenous and total antibiotic duration in children younger than 18 years with bacterial infections.[14] It compared shorter courses with traditionally longer durations. In many conditions such as respiratory, skin and soft tissue and genitourinary infections long durations of intravenous antibiotics might be unnecessary and the switch from intravenous to oral can occur earlier.

When considering a change to oral therapy it is important to evaluate the clinical situation. This includes the response to treatment, the patient's immune status, comorbidities, allergies and their ability to absorb and tolerate oral drugs. Knowing the causative pathogens and resistance patterns is important or, if available, the patient's microbiological results. Regarding the antibiotic to use consider its:

- spectrum of activity
- bioavailability
- penetration to the site of infection
- potential adverse effects.

Australian guidelines

eTG Antibiotic includes guidance for timely switching from intravenous to oral antibiotics. There has to be clinical improvement, resolving fever and no unexplained haemodynamic instability (see Box).[15]

The Australian paediatric infectious diseases community has collaborated in a systematic review of the evidence for switching from intravenous to oral therapy in 36 childhood infections. The aim of the review was to give clinicians the confidence to change children to oral antibiotics and to send them home earlier. It found that for some infections the switch from intravenous therapy can occur sooner than previously recommended.[14]

Prolonged intravenous therapy

Some conditions, such as bone and joint infections and endocarditis, are managed with prolonged

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Box **Guidance for intravenous to oral switch**

It is often appropriate to switch a patient's therapy from the intravenous to oral route when all of the following apply:*

- clinical improvement
- fever resolved or improving
- no unexplained haemodynamic instability
- tolerating oral intake with no concerns about malabsorption
- a suitable oral antimicrobial with the same or similar spectrum, or an oral formulation of the same drug, is available. For children, a suitable paediatric formulation is available.

* Does not apply to infections that require high tissue concentrations or prolonged intravenous therapy (e.g. meningitis, endocarditis).

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courses of intravenous antibiotics. There is little evidence to guide the duration of intravenous therapy and whether oral antibiotics can be used.

Bone and joint infections

The Oral versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA) trial was conducted at multiple centres across the UK.[16] It compared early switching (within one week) from intravenous to oral therapy to continuing intravenous antibiotics for at least six weeks. It included all adults with suspected bone and joint infections, irrespective of surgical intervention or antibiotic choice, who were planned to receive at least six weeks of antibiotic therapy. Comparing the outcomes at one year suggested that appropriately selected oral therapy is non-inferior to intravenous therapy. However, there are several important caveats:

- the trial was not powered to evaluate the outcome between different types of infection
- Gram-negative infections were under-represented
- most patients had surgical management of the infection
- rifampicin was used as a treatment option in approximately one-third of the cohort
- the clinicians managing the patients were specialist-led teams.

Although the events were not necessarily related to the antibiotics, one in four patients experienced a serious adverse event. This shows that ongoing monitoring is still required even with an oral antibiotic regimen.[16,17] Further studies are required to look more closely at the different types of infection and the varying antibiotic regimens. Ideally these trials should be performed in the Australian healthcare system.

Endocarditis

The Partial Oral Treatment of Endocarditis (POET) trial was a study of left-sided endocarditis caused by streptococci, *Enterococcus faecalis*, *Staphylococcus aureus* or coagulase-negative staphylococci. The patients were randomised to either receive intravenous drugs for the full course of therapy, or for a minimum of 10 days followed by oral therapy. Patients were clinically stable before the switch and required transoesophageal echocardiography to confirm the response to treatment. Oral antibiotic regimens were designed to include at least two drugs with different mechanisms of action and were based on pharmacokinetic–pharmacodynamic analyses to enhance synergy and decrease the risk of resistance.[18]

There was no difference in a composite end point of all-cause mortality, unplanned cardiac surgery, embolic events or relapse of bacteraemia from the

primary pathogen. A subsequent analysis at 3.5 years showed similar results.[18,19]

Important caveats on these results included the heterogeneity in the bacterial pathogens being treated and the antibiotic combinations used and the lack of infections with multiresistant organisms. Few patients had cardiac devices or were injecting drug users. The study was also led by physicians in specialist centres.[20]

Antibiotic resistance

The overuse of antibiotics has contributed to the emergence and dissemination of antimicrobial-resistant nosocomial and community pathogens. Reducing intravenous antibiotic use and shortening the duration of antibiotic courses will contribute to overall less antibiotic use and thus may reduce the development of antibiotic resistance. The appropriate use of oral antibiotics, particularly those with good bioavailability, is also essential to maintain their usefulness.

Conclusion

For many infections oral antibiotics can be as effective as intravenous drugs. Shorter durations of intravenous antibiotic therapy and switching to oral therapy should be important considerations in patient management. They have the potential to improve outcomes for patients by avoiding the adverse effects of intravenous drugs and may facilitate early discharge from hospital. ◄

Conflict of interest: none declared

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Antiemetic drugs: what to prescribe and when

SUMMARY

Nausea and vomiting are common symptoms with many possible causes, including the adverse effects of drugs. If a drug is indicated, the cause guides the choice of antiemetic drug.

The main antiemetic classes include antagonists of the serotonin, dopamine, histamine, muscarinic and neurokinin systems, corticosteroids and benzodiazepines. Some antiemetics appear more effective for specific indications.

Serotonin and neurokinin antagonists, such as ondansetron and aprepitant, are highly effective in treating chemotherapy-induced nausea and vomiting. Metoclopramide and antihistamines are first-line options for nausea and vomiting in pregnancy.

Serotonin antagonists and some dopamine antagonists, such as metoclopramide, can prolong the QT interval on the ECG. Dopamine antagonists can cause extrapyramidal adverse effects, particularly in children.

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Introduction

Nausea and vomiting are commonly encountered symptoms with multiple causes. These include infections, cancer, pregnancy and the adverse effects of many drugs.

Physiology

Multiple neurohumoural pathways can induce nausea and vomiting. Key foci include the chemoreceptor trigger zone in the floor of the fourth ventricle and the vomiting centre in the medulla with inputs from the nucleus tractus solitarius and vagus nerve.[1] The emetic response is mediated through multiple neurotransmitters including histamine, dopamine, serotonin, acetylcholine and neurokinin.[2] With the exception of neurokinin, cannabinoids modulate the activity of these neurotransmitters to influence the emetic response.[3]

Classes of antiemetics

The various classes of antiemetics target different pro-emetic pathways to alleviate nausea and vomiting. Some target more than one pathway (Table 1).[1,4-14] The classes of antiemetics include antagonists of dopamine, serotonin, neurokinin, histamine and acetylcholine. The cannabinoid agonists,[3] corticosteroids and benzodiazepines also have antiemetic actions.

Treatment of specific causes of nausea and vomiting

Although a number of antiemetics are suitable for the treatment of nausea and vomiting from a range of conditions (Table 2), there are certain circumstances when one drug may be preferred over another.

Gastroenteritis

Acute gastroenteritis is caused by viral, bacterial or protozoal infections. Therapeutic options available for adults with vomiting secondary to gastroenteritis include dopamine antagonists such as metoclopramide or prochlorperazine and serotonin antagonists such as ondansetron.[15]

Nausea and vomiting resulting from acute gastroenteritis is particularly challenging in children. Until the early 2000s, antiemetics including promethazine, metoclopramide and prochlorperazine were widely used in children, however their use is now controversial due to reports of adverse events including sedation and extrapyramidal reactions.[16]

When an antiemetic drug is indicated, serotonin antagonists such as ondansetron are now recommended in guidelines, such as those published by the Royal Children's Hospital Melbourne.[17] These guidelines recommend a single weight-based dose of oral ondansetron. Children weighing 8–15 kg should receive 2 mg, children weighing 15–30 kg should receive 4 mg and children weighing more than 30 kg should receive 8 mg. Ondansetron is not recommended in children under six months of age or less than 8 kg in weight.[17]

A systematic review reported that oral ondansetron reduced vomiting, hospitalisation and the need for intravenous rehydration in children with acute gastroenteritis.[18] Intravenous ondansetron or metoclopramide also reduced vomiting and hospitalisation. A single study in the review reported that rectal dimenhydrinate was effective at reducing vomiting.[18]

Table 1   **Antiemetics available in Australia**

Class	Mechanisms of action	Pharmaceutical Benefits Scheme restrictions
Dopamine antagonists Benzamides – metoclopramide Benzimidazoles – domperidone Phenothiazines – prochlorperazine,* chlorpromazine* Butyrophenones – droperidol,* haloperidol* Atypical antipsychotics – olanzapine*	Block dopamine type 2 (D2) receptors centrally in the chemoreceptor trigger zone and peripherally in the gastrointestinal tract. Domperidone blocks peripheral D2 receptors only. At higher doses, effects on other receptors are seen. These include blockade of serotonin, histamine, adrenergic and muscarinic receptors.	Metoclopramide (parenteral) – palliative care medicine Metoclopramide and paracetamol combinations – available as non-prescription medicines
Serotonin antagonists Ondansetron Granisetron Palonosetron Tropisetron	Block 5-HT$_3$ receptors in the chemoreceptor trigger zone and gastrointestinal tract.	Ondansetron – chemotherapy or radiation-induced nausea and vomiting Granisetron – chemotherapy or radiation-induced nausea and vomiting Palonosetron – chemotherapy-induced nausea and vomiting Tropisetron – chemotherapy-induced nausea and vomiting
Neurokinin antagonists Aprepitant Fosaprepitant Netupitant Netupitant/palonosetron fixed-dose combination	Block neurokinin type 1 receptors in the central and peripheral nervous system.	Chemotherapy-induced nausea and vomiting
Antihistamines Doxylamine Cyclizine Pheniramine Promethazine	Block H$_1$ receptors Cyclizine, doxylamine, promethazine and pheniramine all block muscarinic receptors. Promethazine also blocks dopamine D2 receptors.	Available as non-prescription medicines
Anticholinergics Hyoscine	Block muscarinic receptors in vestibular nuclei, vomiting centre and higher brain centres.	Hyoscine (parenteral) – palliative care medicine. Hyoscine (oral) – available as non-prescription medicine.
Corticosteroids Dexamethasone	Central inhibition of prostaglandin synthesis and encephalin release. When combined with 5-HT$_3$ antagonists there are reduced serotonin concentrations in the gut and increased sensitivity of 5-HT$_3$ receptors to antiemetics.	Nil
Benzodiazepines Lorazepam	Agonist action at the GABA$_A$ receptor provides anxiolysis. Action at the chemoreceptor trigger zone to suppress the activity of dopamine.	Nil
Cannabinoids [†] Tetrahydrocannabinol Nabilone Dronabinol Nabiximols	Activate cannabinoid CB1 (inhibitory) receptors in the central nervous system and peripheral nervous system to modulate release of neurotransmitters.	Not applicable

* Also block serotonin, histamine, adrenergic and muscarinic receptors
† Not currently registered as antiemetics in Australia
Source: references 1, 4-14

Opioid-induced

The role of antiemetics to manage opioid-induced nausea and vomiting is poorly defined. Evidence is lacking and confounded by studies focused on postoperative nausea and vomiting (where patients were given opioids and anaesthetic drugs). As a result, the choice of antiemetic for opioid-induced nausea and vomiting will depend on factors such as medical comorbidities, the adverse effects of the drug, its cost and the clinician's familiarity with it.

A systematic review reported that low-dose droperidol (less than 4 mg per day) was effective at reducing opioid-induced nausea and vomiting.[19] Ondansetron at doses of 8 mg or 16 mg per day was effective,[20] but metoclopramide is not superior to placebo.[21] The role of serotonin antagonists may be limited because opioid-induced nausea and vomiting is not an indication which is currently subsidised by the Pharmaceutical Benefits Scheme (PBS).

Migraine-related

Migraines are commonly associated with nausea, vomiting and reduced gastrointestinal motility.[1] Due to this impaired motility and delayed drug absorption, parenteral routes of antiemetic administration may be required.[1]

Metoclopramide, a prokinetic antiemetic, reduces the absorption lag time of oral aspirin and non-steroidal anti-inflammatory drugs in patients with migraine.[22,23] In one study it reduced the time for aspirin to reach a maximum plasma concentration, from 24.6 to 18 minutes[22] and reduced the time for tolfenamic acid (not available in Australia) from 2 hours 51 minutes to 2 hours 19 minutes.[23] Additionally in healthy volunteers, administration of metoclopramide with paracetamol resulted in both a higher peak plasma concentration of paracetamol and a shorter time to peak plasma concentration.[24] The average time taken to reach the peak plasma concentration of paracetamol was reduced from 120 minutes to 48 minutes.[24] Consequently, metoclopramide has been incorporated into numerous guidelines as it may be beneficial in reducing nausea while enhancing the efficacy of concurrent analgesics.[1,25]

Dopamine antagonists such as prochlorperazine or chlorpromazine are effective in controlling nausea and vomiting.[26] Data are lacking on the efficacy of serotonin antagonists in migraine.

Pregnancy

Nausea and vomiting are common during the first trimester of pregnancy, affecting up to 90% of women.[27] If drug treatment is needed, antihistamines

Table 2   **Indications and scheduling for antiemetic drugs**

Indication	Therapeutic options (Scheduling)
Gastroenteritis	Dopamine antagonists (S4)
	Serotonin antagonists (S4)
Opioid-induced nausea and vomiting	Serotonin antagonists (S4)
	Dopamine antagonists (S4) • droperidol
Migraine-related nausea and vomiting	Dopamine antagonists (S4) • metoclopramide with paracetamol (S3) • metoclopramide (S4) • prochlorperazine (S3 or S4)
Vestibular causes of nausea and vomiting	Antihistamines (S3)
	Anticholinergics (S3)
	Dopamine antagonists (S4)
Chemotherapy-induced nausea and vomiting	Serotonin antagonists (S4)
	Neurokinin-1 antagonists (S4)
	Corticosteroids (S4) • dexamethasone
	Dopamine antagonists (S4) • olanzapine, haloperidol
	Benzodiazepines (S4) • lorazepam
Radiation-induced nausea and vomiting	Serotonin antagonists (S4)
	Corticosteroids (S4) • dexamethasone
	Dopamine antagonists (S4)
Postoperative nausea and vomiting	Dopamine antagonists (S4)
	Serotonin antagonists (S4)
	Antihistamines (S3)
	Corticosteroids (S4) • dexamethasone
	Neurokinin-1 antagonists (S4)
	Benzodiazepines (S4) • lorazepam

S3 pharmacist-only medicine
S4 prescription-only medicine

including doxylamine and diphenhydramine are efficacious, without an increased risk of congenital malformations.[27] Metoclopramide is also effective with no increased risk of congenital malformation, spontaneous abortion or reduced birthweight.[28] Other dopamine antagonists are not recommended due to conflicting evidence of safety during pregnancy.

The use of serotonin antagonists, such as ondansetron, in pregnancy has been increasing. However, ondansetron has limited safety data. A 2018 study reported no increased risk of cardiac malformation, but a slightly increased risk of oral clefts.[29] Ondansetron is therefore not recommended as a first-line treatment.

Vestibular disorders including motion sickness

Nausea and vomiting from conditions such as benign paroxysmal positional vertigo and motion sickness are due to stimulation of the vomiting centre via the vestibular nuclei. The primary neurotransmitters involved in this pathway are histamine receptors and acetylcholine muscarinic receptors.[1] The main treatments are therefore antihistamines such as promethazine, anticholinergics such as hyoscine, and dopamine antagonists such as prochlorperazine.[1,30]

Palliative care

The causes of nausea and vomiting in palliative care can broadly be divided into:

- disease state-related (e.g. cancer burden, ileus, uraemia in kidney disease or gastrointestinal oedema in heart failure)
- treatment-related (e.g. chemotherapy-induced or opioid-induced)
- biochemical (e.g. hypercalcaemia)
- toxin-mediated (secondary to anorexia-cachexia syndrome).[13]

Evidence to guide the choice of antiemetics in palliative care is lacking. Metoclopramide 10 mg three times daily is effective in up to 40% of cases.[13] Haloperidol 1.5–5 mg daily is effective in up to 47% of cases,[31] while chlorpromazine 25 mg four times daily is effective in up to 70% of cases.[32] Olanzapine 2.5–7.5 mg daily is also considered effective, but the precise response rate is unknown.[33] Adverse reactions such as sedation and anticholinergic effects, particularly with olanzapine and chlorpromazine, may limit the usefulness of dopamine antagonists.[13]

There are conflicting data on the use of serotonin antagonists in refractory nausea and vomiting in palliative care. In a single randomised trial, tropisetron was more effective than metoclopramide or chlorpromazine, even when they were combined

with dexamethasone. The combination of tropisetron, dexamethasone and chlorpromazine was most effective.[34] However, another trial examining opioid-induced nausea and vomiting in palliative care reported that ondansetron was not more effective than metoclopramide or placebo.[35] There are no randomised trials examining the efficacy of antihistamines, however an uncontrolled study based on patient reports suggested cyclizine had efficacy.[13,36]

Anticholinergics such as hyoscine are used in palliative care, but not primarily for nausea. They are often prescribed for excessive gastric secretions and in terminal bowel obstruction.[13]

Corticosteroids such as dexamethasone (4–8 mg daily) are effective at managing chemotherapy-induced nausea and vomiting, bowel obstruction and raised intracranial pressure.[13] Dexamethasone, at doses as low as 2 mg daily, enhances the control of nausea and vomiting when added to combination treatment with tropisetron and either metoclopramide or chlorpromazine.[34]

Chemotherapy-induced

The emetogenic potential of chemotherapy drugs varies. For example, nausea and vomiting resulting from low emetogenic chemotherapy, such as paclitaxel, can be treated with a serotonin antagonist, while highly emetogenic chemotherapy, such as cisplatin, will require a combination of a serotonin antagonist, neurokinin antagonist and dexamethasone.[12]

Haloperidol and olanzapine are effective for chemotherapy-induced nausea and vomiting.[37] Olanzapine is now recommended as part of first-line management of highly emetogenic chemotherapy.[9,38]

Antihistamines, metoclopramide and prochlorperazine are less effective in chemotherapy-induced nausea and vomiting. Benzodiazepines such as lorazepam may be used as adjunctive therapy. They function to reduce anxiety and anticipatory nausea and vomiting.[39] There is a lack of data regarding the use of anticholinergics.[4]

While not registered in Australia, cannabinoid products have been tried for chemotherapy-induced nausea and vomiting. A systematic review concluded that cannabinoids were superior to placebo but not prochlorperazine. The data were inadequate to determine efficacy compared to metoclopramide, domperidone or chlorpromazine.[40] Cannabinoids have not been compared to newer antiemetics such as serotonin or neurokinin antagonists. They may have a role for patients with chemotherapy-induced nausea and vomiting that fails to respond to first-line treatment.[40] However, cannabinoids are only available through the Special Access Scheme.

Radiation-induced

The severity of radiation-induced nausea and vomiting depends on the irradiated body area. For example, total body irradiation has a high risk of nausea and vomiting and requires combination treatment with a serotonin antagonist and dexamethasone. Radiation to the head and neck has a lower risk and can be managed with a serotonin antagonist alone.[41]

Serotonin antagonists are more effective than dopamine antagonists alone or in combination with dexamethasone. Adding dexamethasone to a serotonin antagonist further reduces radiation-induced nausea and vomiting.[42]

Postoperative

A systematic review found that serotonin antagonists (ondansetron, granisetron and tropisetron), dexamethasone, droperidol and cyclizine were all more effective than placebo for the treatment of postoperative nausea and vomiting.[19] Depending on the clinical situation, certain antiemetics may need to be avoided. For example, given the constipating effect of serotonin antagonists, they should either be avoided or used with caution in patients at high risk of intestinal obstruction, as they may worsen or mask a progressive ileus.

Metoclopramide, at the standard 10 mg dose, is less effective than serotonin antagonists[43] and no more effective than placebo.[44] Although doses of metoclopramide greater than 25 mg may be more effective,[45] the increased risk of adverse events such as dystonia limit its use.

A recent study demonstrated that benzodiazepines such as lorazepam may be beneficial at reducing postoperative nausea and vomiting. Compared with placebo, 1 mg of orally administered lorazepam 60 minutes before general anaesthesia significantly reduced both postoperative nausea and vomiting and the requirement for antiemetic treatment during the postoperative period.[46]

Studies have also demonstrated that neurokinin antagonists such as aprepitant are effective at reducing postoperative nausea and vomiting.[47] However, they are not currently PBS subsidised for this indication.

Adverse effects

The mechanisms of action of antiemetics, such as antagonising neurotransmitters, contribute to some of their adverse effects.

QT prolongation

The risk of prolonging the QT interval on the ECG is important to consider when prescribing antiemetic drugs. While the effect may not be significant in isolation, the risk of dysrhythmia increases with other risk factors affecting the QT interval, such as drugs, hypokalaemia and hypocalcaemia.

Serotonin antagonists cause a reversible dose-dependent prolongation of the QT interval.[4] While this is a class effect, the risk varies among drugs. Both ondansetron and granisetron prolong the QT interval when administered intravenously at doses over 8 mg and 10 micrograms/kg respectively. However, there have been no reports of QT prolongation following oral administration.[48,49] Palonosetron and tropisetron are not associated with QT prolongation.[4,50]

A systematic review in children did not report any major adverse events with the use of serotonin antagonists such as ondansetron.[18] However, it is important to note that there have been multiple cases of cardiac arrhythmia or death in children associated with repeated administration of parenteral ondansetron.[51]

Dopamine antagonists cause QT prolongation and the US Food and Drug Administration (FDA) has issued 'black box' warnings for droperidol and haloperidol. However, the Australian DORM[52] and DORM-2[53] studies did not report an increased rate of QT prolongation with parenteral droperidol 10 mg compared to midazolam. Additional evidence suggests that higher doses of droperidol, up to 20–30 mg, are not always associated with QT prolongation.[54] Furthermore, as the dose needed to achieve an antiemetic effect is less than 4 mg/day,[55,56] the risk is insignificant. Haloperidol prolongs the QT interval at cumulative intravenous doses as low as 2 mg,[57] but the usual antiemetic dose is 1 mg.[4]

Other dopamine antagonists including metoclopramide, chlorpromazine and prochlorperazine are associated with QT prolongation,[4] but the minimum dose that causes ECG changes is unknown. Domperidone causes QT prolongation, but a recent randomised controlled trial in healthy volunteers found no effect on QT interval for doses as high as 80 mg per day.[58] However, remaining within the recommended dose and exercising additional caution is required in the older patient who may be at increased risk of adverse events compared with a healthy volunteer. Olanzapine has no effect on the QT interval at therapeutic doses.[59]

Extrapyramidal symptoms

There is a range of possible extrapyramidal effects including dystonia, akathisia and parkinsonism,[60] and the risk is greater with rapid intravenous administration. They are mediated through blockade of dopamine receptors in the substantia nigra and striatum.[61] The incidence of extrapyramidal symptoms in patients treated with metoclopramide is 4–25%, while the incidence with prochlorperazine is

25–67%[62] increasing with higher doses. These highly variable rates reflect a wide range of antiemetic doses, varying routes of administration and different rates of administration, such as a bolus injection versus intravenous infusion. There is an increased risk of tardive dyskinesia in patients treated with metoclopramide for more than 12 weeks.[4]

The FDA issued warnings about droperidol and haloperidol because of the risk of extrapyramidal symptoms. An incidence of 1–4% is reported after acute administration of droperidol, but this was not reported in the DORM-2 study.[53] Haloperidol has a higher incidence of extrapyramidal symptoms, even at doses under 4 mg.[63] Olanzapine, at doses of 5–20 mg, has also been associated with extrapyramidal symptoms.[63]

In case reports, serotonin antagonists including ondansetron have been associated with extrapyramidal symptoms. These occurred with repetitive intravenous doses of ondansetron totalling 7.5–37.5 mg daily.[64] While it has been suggested that intravenous doses as low as 4 mg may be sufficient to precipitate extrapyramidal symptoms,[64] the association is inconsistent.

Due to the risk of extrapyramidal symptoms, particularly with dopamine antagonists at higher doses, caution is required in the older patient, particularly those with Parkinson's disease. An option for these patients is domperidone, a peripherally acting dopamine antagonist that does not cross the blood–brain barrier.[1] Dopamine antagonists should be avoided in children due to the high incidence of extrapyramidal symptoms, particularly dystonic reactions.

Sedation

Dopamine antagonists are commonly associated with sedation. While in certain circumstances sedation may be a desired effect, it can limit the usefulness of these drugs as antiemetics. In psychosis, droperidol is more sedating than both olanzapine and haloperidol, however the doses are higher than those required for antiemetic use.[65] At doses of 0.25–1.25 mg, droperidol caused sedation in up to 17% of cases.[66] Low-dose olanzapine (2.5–7.5 mg) is associated with sedation in 20% of cases, while haloperidol is reported to cause sedation in up to 21% of cases at doses of 1–5 mg daily.[67]

Chlorpromazine, prochlorperazine and metoclopramide are associated with sedation, but the precise rate is uncertain. Antihistamines such as doxylamine, cyclizine or promethazine are also associated with sedation. Promethazine is more sedating than either metoclopramide or prochlorperazine.[68-70]

Serotonin antagonists are typically thought to be non-sedating, however a randomised trial reported that ondansetron may be as sedating as metoclopramide, but less than promethazine.[69] Benzodiazepines and cannabinoids cause significant sedation which may limit their use as antiemetics.[40]

Anticholinergic effects

Many antiemetic drugs have anticholinergic adverse effects including confusion, delirium, hallucinations, visual disturbance, urinary retention, constipation and tachycardia. In older patients, anticholinergic adverse effects are associated with an increased risk of developing cognitive impairment, falls and all-cause mortality.[71] Dopamine antagonists,[72] antihistamines[4] and hyoscine are known to have anticholinergic effects. Dopamine antagonists such as chlorpromazine and olanzapine, and antihistamines such as doxylamine and promethazine are likely to pose the greatest risk.

Constipation

Constipation is a well-described adverse reaction to serotonin antagonists such as ondansetron and anticholinergic drugs such as hyoscine.[4] Dopamine antagonists such as metoclopramide and domperidone are prokinetic so may be a better choice for patients with constipation.

Conclusion

While numerous antiemetics are available and broadly useful, the choice of a particular drug in an individual patient can vary depending on numerous considerations. These include the age of the patient, the indication for treatment, pregnancy, medical comorbidities and the risk of adverse effects. ◄

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Prescribing in renal supportive care

SUMMARY

Renal supportive care incorporates the principles of palliative care into the management of patients with advanced kidney disease. Its focus is on improving the quality of life for patients with a high burden of symptoms.

Common problems include pain, restless legs syndrome and uraemic pruritus. Symptom management must involve patient participation, education and non-pharmacological strategies to address both physical and psychosocial problems, and to prioritise patient-centred goals.

The patients are medically complex and polypharmacy is common. When prescribing, it is important to consider the altered pharmacokinetics, potential drug interactions and the clearance of drugs by dialysis.

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Introduction

Renal supportive care is a relatively new activity that incorporates the principles of specialist palliative care within the standard care of patients with advanced chronic kidney disease. This is relevant for patients receiving haemodialysis or peritoneal dialysis who have a high burden of physical and psychological symptoms. It is also suitable for patients with end-stage kidney disease who are being conservatively managed without dialysis.

Patients needing renal supportive care tend to be older, have a high symptom burden and multiple comorbidities. Patient-centred goals, such as enhancing quality of life, symptom management and psychosocial support, are therefore the priorities of care. Treatment strategies must be flexible, practical and holistic, incorporating non-pharmacological and pharmacological options and addressing multiple facets including physical, psychosocial and spiritual domains.

General prescribing principles

Prescribing drugs in renal supportive care can be challenging. End-stage kidney disease alters the pharmacokinetics of renally eliminated drugs, leading to a risk of accumulation and toxicity. Adjusting doses and dosing intervals is necessary to ensure safety while maintaining efficacy. Some commonly used drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated in end-stage kidney disease. Multiple comorbidities lead to polypharmacy, and drug interactions are common. Prescribing differs for haemodialysis, peritoneal dialysis and conservative management because some drugs can be removed by haemodialysis or (less commonly) peritoneal dialysis.

Most drugs with significant renal elimination must be used cautiously but are not always contraindicated.

A general rule is to start with the lowest dose, use longer dosing intervals and increase the dose slowly while monitoring for efficacy and features of toxicity. Drugs cleared by haemodialysis should be given after haemodialysis.

Common symptoms

Symptoms place a large burden on patients with advanced kidney disease and their families. Treatments should be directed towards the patient's priorities, take account of their preferences and be feasible. The goals should be achievable.

Pain

Pain is common in chronic kidney disease and usually attributable to one or more comorbidities. It is helpful to distinguish nociceptive pain caused by tissue injury from neuropathic pain caused by nerve damage, giving a tingling, burning, stabbing or shooting sensation. The experience and impact of pain varies between patients. Chronic pain is often associated with significant physical and psychosocial consequences.

Treatment strategies must incorporate education, patient participation and evaluation. They should focus on patient-centred goals, especially if the underlying pathology cannot be corrected. If possible, the cause of the pain should be identified, as some causes have specific therapy, such as urate lowering for gout, facet joint injections, or antiangina drugs for coronary ischaemia.

Non-drug therapy

For localised pain, heat and cold packs are helpful, as are joint splints or a walking aid. Physiotherapy, hydrotherapy, exercises (both gentle aerobic and resistance training)[1] and weight reduction are effective for chronic musculoskeletal pain.

Drug therapy

Systemic NSAIDs are contraindicated, but a topical NSAID such as diclofenac can be used for localised musculoskeletal pain.

Systemic treatment should follow the World Health Organization analgesic ladder,[2] with a stepwise approach beginning with non-opioids, and progressing to opioids with adjuvants. Paracetamol is the initial analgesic of choice in chronic kidney disease. There is no dose modification and paracetamol remains a useful background treatment even when opioids are required. Opioids must be used carefully in renal supportive care, given their narrow therapeutic window and potential for accumulation and toxicity (Table).[3,4] For moderate to severe pain that has not responded to non-opioid drugs and is detrimental to physical function and quality of life, short-acting opioids can be considered. They are started at a low dose and slowly titrated up according to pain relief and adverse effects.[3]

Adjuvant therapy should be added for severe or refractory nociceptive pain, or used as initial therapy for neuropathic pain. Gabapentin and pregabalin, calcium channel alpha-2-delta ligands (or gabapentinoids), are efficacious and have multiple uses in renal supportive care. They are the preferred initial therapy for neuropathic pain. Due to their almost exclusive renal elimination, substantial dose reductions are needed. Monitoring for the common adverse effects of somnolence, dizziness and gait disturbance is important. Start therapy with gabapentin 100 mg or pregabalin 25 mg on alternate nights for conservative management and peritoneal dialysis, and three times weekly after haemodialysis for patients having haemodialysis.[3] Increases to the dosing frequency (to nightly and twice daily) or the dose (up to gabapentin 300 mg or pregabalin 75 mg/24 hours) should occur one week apart while monitoring for adverse effects. Higher doses may be tolerated in some patients, but specialist advice should be sought.

Tricyclic antidepressants, such as amitriptyline, can be used to manage neuropathic pain.[3] Serotonin and norepinephrine reuptake inhibitors such as duloxetine can also be used.[3,5]

Table   **Opioid use in end-stage kidney disease**

Opioid	Renal clearance	Formulation	Starting dose	Comments
Hydromorphone	Small amount excreted in urine: needs dose reduction Cleared by haemodialysis	Oral: • liquid • immediate-release tablet • sustained-release tablet	Immediate-release oral hydromorphone starting at 0.5 mg as required 4 times daily as liquid formulation Dose after haemodialysis	Used for severe acute pain. Long-acting oral hydromorphone can accumulate and lead to toxicity and should be used only when a stable daily dose is established (or switch to fentanyl patch instead for maintenance).
Oxycodone	Small amount excreted in urine: needs dose reduction Cleared by haemodialysis	Oral: • immediate-release tablet • sustained-release, with or without naloxone	Immediate-release oral oxycodone starting at 2.5 mg as required 4 times daily Dose after haemodialysis	Used for severe acute pain. Start slow release only after a stable daily dose is established.
Fentanyl	Minimal renal elimination: no dose reduction required	Patch applied to skin	Not recommended in opioid-naïve patients	Onset of action usually 8–12 hours after first patch application. Useful for background analgesia once pain controlled with hydromorphone or oxycodone.
Buprenorphine	Minimal renal elimination: no dose reduction required	Patch applied to skin	Start with 5 mg patch changed every week	Onset of action usually 12–24 hours after initial patch application. Useful for background analgesia. Can be started in opioid-naïve patients.

Additional notes:

Morphine and codeine are best avoided in renal supportive care as active metabolites accumulate in renal failure and lead to clinically significant toxicity including sedation, confusion, myoclonus, and respiratory depression.

Tramadol (maximum 50 mg twice a day) and tapentadol (maximum 50 mg twice a day) can be used at low doses and with caution due to multiple potential drug interactions, unpredictable risk of overdose, and the risk of serotonin syndrome with concomitant use of some antidepressants. May provide additional benefits in neuropathic pain.[4]

Methadone has minimal renal elimination and can be used in renal supportive care without dose adjustment. However, due to its long half-life, specialist advice is recommended when starting methadone in the community.[4]

Source: references 3 and 4

Restless legs syndrome

Restless legs syndrome is a sensorimotor disorder characterised by an overwhelming urge to move the legs, predominantly during periods of inactivity. It is temporarily relieved by movement. Patients typically describe achy, creeping, crawling or itchy sensations in the legs.[6] Restless legs syndrome is prevalent in patients having dialysis (12–25%) but also affects other patients with chronic kidney disease. It is associated with reduced quality of life, anxiety, insomnia, daytime sleepiness and premature stopping of dialysis.[7]

Non-drug therapy

Aerobic exercises such as walking and stretching may be helpful. Exacerbating substances such as nicotine, alcohol, and caffeine should be avoided.

Drug therapy

Avoid drugs such as dopamine antagonists (typically antipsychotics and metoclopramide), antihistamines and serotonergic antidepressants. Correcting iron deficiency may be helpful.

Gabapentinoids are first-line drug therapy for restless legs syndrome. An extra dose can be taken one hour before haemodialysis if the patient is symptomatic during haemodialysis.

Non-ergot dopamine agonists are also efficacious for restless legs syndrome.[7] Ropinirole (compared to pramipexole) has less accumulation in renal failure and can be started at 0.25 mg at night and titrated up to 2 mg at night.

Uraemic pruritus

Uraemic pruritus is an itch affecting large bilateral symmetrical surface areas with no associated primary skin lesion. It can be generalised or localised to the back, face and arms.[8] Uraemic pruritus is associated with depression and reduced quality of life, and exacerbates sleep problems.[6] Non-uraemic causes of pruritus, such as dry skin, drug reactions, scabies or fungal skin infections, should not be overlooked.

Good skin care is essential,[6] as dry skin exacerbates itch. It is helpful to avoid long, hot showers and harsh soaps, and to moisturise within minutes of washing while the skin is still damp. Aqueous cream emollient and baby oil are effective in reducing uraemic pruritus and improving quality of life if applied 2–4 times daily.[6]

If the itch is localised, capsaicin 0.025% can be applied topically. Although effective, it can cause burning[8] and applying topical menthol beforehand may improve tolerability.

In more generalised uraemic pruritus, gabapentinoids have the strongest supporting evidence.[8,9] Alternatives include sertraline 50 mg daily, doxepin 10 mg twice daily and evening primrose oil (affects gamma linoleic acid) starting at one capsule (1000 mg) at night, up to two capsules twice daily.[6]

For unresponsive uraemic pruritus, non-uraemic causes need to be reconsidered. Once these are excluded, treatment with ultraviolet B light can be effective.[8]

Fatigue

In renal supportive care fatigue is the most common symptom. Its cause is multifactorial, so management involves identifying and addressing contributing factors:

- iron deficiency or the anaemia of chronic kidney disease – can be corrected with iron supplements and erythropoietin-stimulating drugs
- vitamin D deficiency – can be managed with oral supplementation
- metabolic acidosis – should be corrected with oral sodium bicarbonate
- mood disorders such as anxiety and depression – should be assessed and treated
- obstructive sleep apnoea – should be assessed and treated
- sleep disturbances
- drugs that exacerbate fatigue, including benzodiazepines, gabapentinoids, beta blockers, centrally acting antihypertensives and sedating antidepressants (such as mirtazapine).

After addressing reversible factors, patients should be counselled regarding maintaining good nutrition, regular exercise and practical energy conservation strategies. For patients taking drugs causing fatigue, management needs to be negotiated with the patients as to the indications for these drugs, alternatives and treatment goals.

Sleep disturbances

A variety of symptoms can contribute to poor sleep. These include restless legs syndrome, uraemic pruritus, anxiety, depression, nocturia and chronic pain. These should be explored and treated when possible. Nocturia can be managed by taking diuretics early in the day and avoiding fluid, alcohol and caffeine in the evenings. In men, treat any comorbid prostate pathology.

Educating patients regarding good sleep hygiene can foster self-management. Sleep hygiene and cognitive behavioural therapy should be the mainstay of treatment. Drugs such as temazepam and zopiclone should be limited to short-term use. Melatonin is another option, but its efficacy is also limited to short-term use.[10]

Nausea

While metabolic disturbances in uraemia can cause nausea, other contributing factors are common:

- drugs, particularly opioids, dopamine agonists and some antidepressants
- gastroparesis, commonly from comorbid diabetes, can lead to delayed gastric emptying, and worsening reflux symptoms
- constipation.

Non-drug therapy

Smaller, frequent meals, good oral hygiene and maintaining an upright posture after meals to minimise reflux are important. Constipation should be managed.

Drug therapy

Dopamine antagonists, such as domperidone, have prokinetic effects and are best given 30 minutes before meals. Metoclopramide or low-dose haloperidol (0.5–1 mg) can be substituted and have additional CNS effects on nausea. However, they can have extrapyramidal adverse effects during long-term use and should be avoided in patients with restless legs syndrome, especially if they are taking dopamine agonists. Antihistamines such as cyclizine, and serotonin ($5HT_3$) antagonists such as ondansetron may be used but can be costly for patients.

Taste changes

Common changes in chronic kidney disease include a metallic or bitter taste, lack of taste in food, and a dry mouth. This can affect appetite, nutrition and the enjoyment of food.

Sodium bicarbonate mouthwash can improve taste and dry mouth. It is cheap and simple to make – one teaspoon of sodium bicarbonate in 500 mL water. This mouthwash should be used regularly during the day, usually every four hours. Other helpful habits include:[11]

- a glass of soda water before meals
- avoiding foods that give bitter tastes such as red meat, and tea or coffee
- adding sweet or sour flavours such as sugar, vinegar, fruits, or lemon to relieve bitterness
- adding herbs and spices, including chilli, to give extra flavour to food
- peppermints and chewing gums to help stimulate saliva and improve taste.

Conclusion

Prescribing for patients receiving renal supportive care requires a flexible and nuanced approach, taking into consideration altered pharmacokinetics, polypharmacy, comorbidities and practicality. Management of these patients' complex care requires using both non-pharmacological and pharmacological therapies focussing on patient-centred goals. ◄

Conflict of interest: none declared

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The perils of antiepileptic toxicity

Case study

A 63-year-old high-level-care nursing home resident was brought to hospital with reported 'seizures' at the facility. He had been increasingly lethargic and non-verbal for four days. The man had a history of epilepsy related to traumatic brain injury, alcohol-associated pancreatitis and Wernicke-Korsakoff's syndrome. He was cachectic. His regular treatment included valproate 1.5 g twice daily and levetiracetam 1.5 g twice daily.

Non-convulsive status epilepticus was suspected after a failure to regain consciousness. This was the provisional diagnosis as an EEG eight months previously was reported as showing non-convulsive status epilepticus.

The patient was given intravenous doses of valproate (800 mg), levetiracetam (1.5 g) and phenytoin (1.2 g) in the emergency department. Before administration of these loading doses his total valproate concentration was 62 mg/L, which is within the therapeutic range.

Over the subsequent two weeks, the patient remained unresponsive with no observed seizures. As this was assumed to be because of non-convulsive status epilepticus, twice daily phenytoin (200 mg) and lacosamide (100 mg) had been added to his treatment. EEGs showed moderate–severe diffuse cortical dysfunction, but no electrographic seizure activity. Repeat total plasma concentrations on day 16 showed phenytoin 16 mg/L and valproate 21 mg/L.

In a review of the case, hypoalbuminaemia-adjusted total drug concentrations were calculated because phenytoin and valproate are both highly protein-bound drugs with the potential for concentration-dependent toxicity. His albumin on admission had been 23 g/L. The Figure shows the measured and hypoalbuminaemia-adjusted total drug concentrations.[1,2] Given the correlation of the patient's clinical state and these results, it was realised that the patient had anticonvulsant toxicity.

Following cessation of phenytoin and reduction of the valproate dose, the patient recovered to his usual state. He was able to return to the residential care facility.

Comment

This case highlights concerns regarding recognising antiepileptic toxicity and interpreting drug concentrations in patients with hypoalbuminaemia, hepatic dysfunction and drug interactions.

The goal of antiepileptic therapy is to maximise seizure control and minimise adverse effects. As treatment aims to prevent seizures, it is difficult to clinically assess the lowest effective maintenance dose for long-term seizure control or recognise signs of toxicity.[3] It is possible that the cause of the patient's increasing lethargy before admission was emerging anticonvulsant toxicity.

Phenytoin and valproate are both highly protein-bound drugs (>90%) with non-linear pharmacokinetics, saturable protein binding and complex drug interactions.[2] The free unbound component of the drugs is responsible for their antiepileptic activity and neurological and systemic toxicity. The risk of toxicity increases with the severity of hypoalbuminaemia. With both antiepileptics, toxicity may present as central nervous system depression, cerebellar dysfunction, seizures, hepatotoxicity and bone marrow abnormalities (Table).[3,4]

Valproate inhibits phenytoin metabolism and causes displacement of phenytoin from albumin, so it increases free phenytoin concentrations. Phenytoin induces valproate metabolism. This explains the decrease in valproate concentration once phenytoin was added and the significant increase once phenytoin was ceased (Fig.).[3]

Monitoring

Therapeutic drug monitoring is the measurement of drug concentrations with appropriate interpretation to influence prescribing.[3] While commonly used to assess adherence, it is also useful when suspecting toxicity, establishing optimal drug dosing when starting therapy, adjusting doses or when using drugs that may interact. Monitoring is especially important for individuals with altered pharmacokinetics including patients with hypoalbuminaemia, underlying organ dysfunction and those at extremes of age or during pregnancy.[3]

Plasma concentrations of antiepileptic drugs correlate with adverse effects and for hypoalbuminaemic patients, free drug concentrations correlate better than total concentrations. Free concentrations more accurately reflect the amount of active drug within the brain.[3] The upper limit of the reference range reflects the concentration above which there is an increased risk of toxicity (Table).[4]

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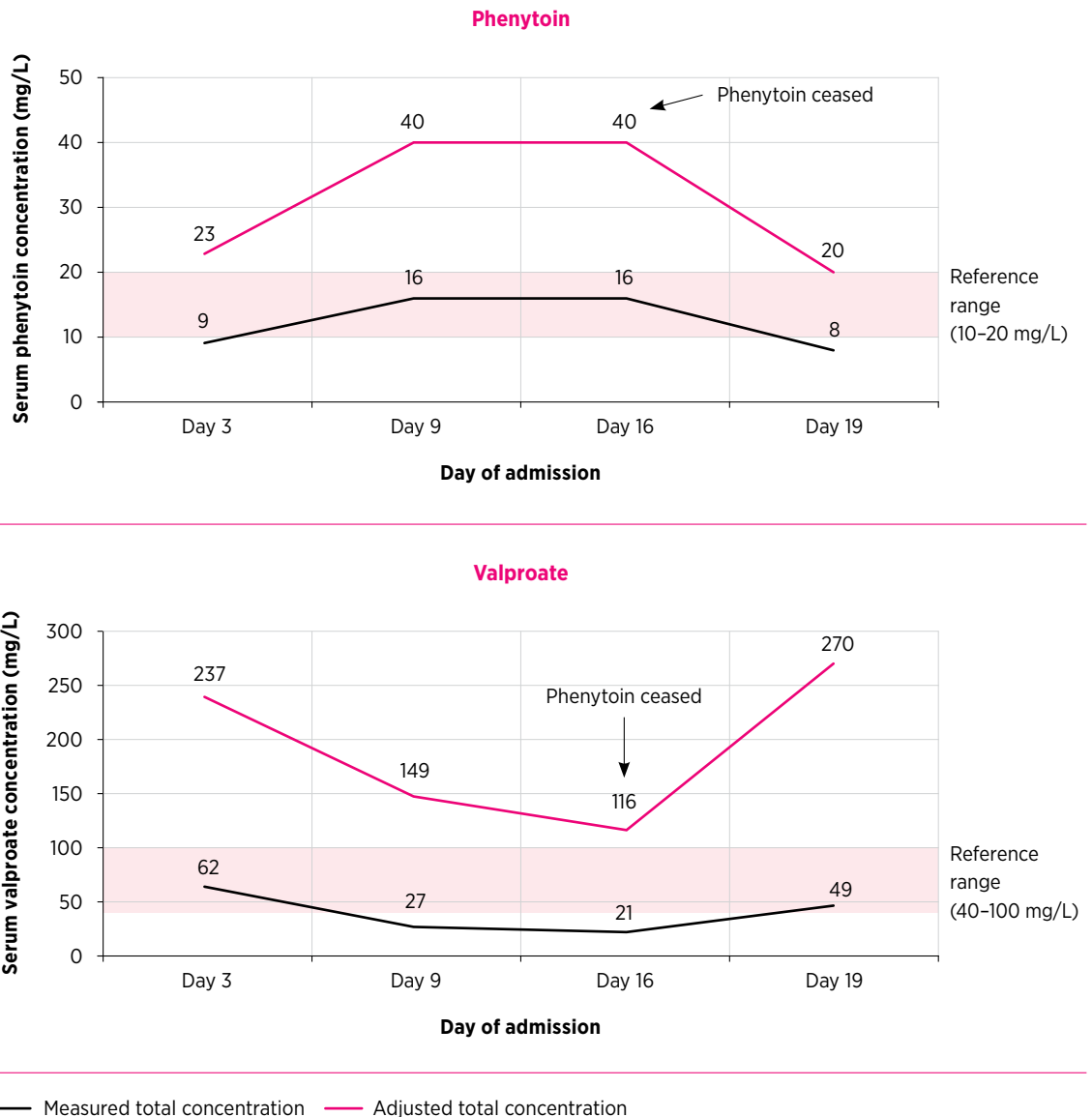Royal Brisbane and Women's Hospital, Brisbane

Fig. **Antiepileptic toxicity in a patient with hypoalbuminaemia**

Phenytoin

Valproate

Measured total concentration   Adjusted total concentration

Conclusion

While therapeutic drug monitoring for phenytoin and valproate is widely available, most Australian laboratories measure total rather than free concentrations as it is faster and less expensive. However, the pharmacokinetic implications of hypoalbuminaemia may result in toxicity despite anticonvulsant concentrations within the therapeutic range. The Sheiner-Tozer equation for phenytoin and the Hermida-Tutor equation for valproate may be used to adjust the total concentrations for hypoalbuminaemia. However, these adjustments may still underestimate total and free drug concentrations in critically ill patients or those with multiorgan dysfunction.[1,2] Our recommendation is to measure free drug concentrations in hypoalbuminaemic patients to monitor for potential drug-related toxicity. It is also important to remember that adverse drug reactions can present as new clinical problems.

Conflict of interest: none declared

Table **Correlation of total plasma concentration and clinical features of toxicity for phenytoin and valproate**

	Clinical features of toxicity
Phenytoin	
10–20 mg/L	Therapeutic range
>20 mg/L	Nystagmus and ataxia
>30 mg/L	Severe ataxia, dysarthria, hyperreflexia, drowsiness, nausea and vomiting
>50 mg/L	Extreme lethargy, coma, paradoxical seizures Cardiac conduction abnormalities with intravenous administration only
Valproate	
40–100 mg/L	Therapeutic range
>100 mg/L	Mild drowsiness and ataxia Variable central nervous system depression
>500 mg/L	Usually coma and metabolic abnormalities
>1000 mg/L	Life-threatening multiorgan dysfunction – metabolic abnormalities, cerebral oedema, bone marrow suppression
>2000 mg/L	Death expected without urgent haemodialysis

Source: reference 4

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DENTAL NOTE

Managing acute dental pain without codeine

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Related article:
Management of dental pain in primary care.
Aust Prescr 2020;43:39–44

Opioids have a limited role in general dental practice. Non-steroidal anti-inflammatory drugs (NSAIDs) are superior to opioids for dental pain[1,2] and are therefore recommended as first line in Therapeutic Guidelines: Oral and Dental.[3] NSAIDs inhibit the prostaglandins responsible for the inflammatory mediators that drive the postoperative pain, swelling and hyperalgesia after procedures such as extractions.

Opioids only interrupt the nociceptive pathway to inhibit pain perception and do not target inflammation. Despite this, Australian dental opioid prescribing has increased in recent years.[4] A recent survey showed that 16–27% of dentists would preferentially use an opioid or paracetamol instead of NSAIDs for pain relief.[5]

Codeine has limited efficacy for dental pain. A recent double-blind randomised-controlled trial investigated the effectiveness of adding codeine to standard analgesic doses of paracetamol and ibuprofen after surgical removal of impacted mandibular third molars. It reported that additional high-dose codeine (60mg) did not reduce pain scores compared to paracetamol and ibuprofen alone.[6] In addition, a randomised, double-blind, placebo-controlled trial showed that combinations of varied doses of paracetamol with ibuprofen provided superior pain relief after impacted third molar surgical extractions, compared to paracetamol with codeine.[7] Patients who took codeine combination products also experienced more adverse effects compared with patients who received ibuprofen and paracetamol combinations.[7]

Codeine is a prodrug that is transformed by cytochrome P450 2D6 into morphine, resulting in the analgesic effect.[1] Approximately 6–10% of Caucasians and 1–2% of Asians have two non-functional alleles of this enzyme so codeine will not provide effective analgesia for these patients.[8] In contrast, up to 10% of Caucasians, 1–2% of Asians and 21% of people from the Middle East are ultra-rapid metabolisers and can generate very high concentrations of morphine from codeine, which may lead to toxicity.[8] In addition, due to pharmacogenomic variability, differences in metabolism and concerns about toxicity, codeine is contraindicated in children under 12 years old, those under 18 years old undergoing an adenoidectomy or tonsillectomy, and in breastfeeding women. There is also the risk of dependence.

Opioids are not first-line drugs for dental pain. As there are established superior alternatives, codeine and other opioids have limited use in general dental practice.

Conflict of interest: none declared

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Letters to the Editor

Atrial fibrillation – QT interval and catheter ablation

The recent article about atrial fibrillation[1] states that the QT interval should be closely monitored, and sotalol is relatively contraindicated in patients with chronic renal impairment. How do we monitor QT interval in atrial fibrillation when it is not measurable?

Linda Mann
General practitioner, YourDoctors, Sydney

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1. McCallum CJ, Raja DC, Pathak RK. Atrial fibrillation: an update on management. Aust Prescr 2019;42;186-91. https://doi.org/10.18773/austprescr.2019.067

Great article on atrial fibrillation[1], but why is there no mention of cryoablation when radiofrequency ablation was mentioned?

Paul Salmon
Radiologist, Sydney

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1. McCallum CJ, Raja DC, Pathak RK. Atrial fibrillation: an update on management. Aust Prescr 2019;42;186-91.

Deep Chandh Raja, one of the authors of the article, comments:

In response to Linda Mann's query, we suggest measuring the QT interval in atrial fibrillation as an average over five ventricular beats. This has been shown to correspond very closely to the QT interval of the same patients in sinus rhythm, when corrected for heart rate.[1] A heart rate correction formula (e.g. Bazett's) should be used, however there is no robust evidence to show superiority of one particular formula over the other.[1]

With regards to the query from Paul Salmon about catheter ablation, there are different sources of energy for catheter ablation – radiofrequency energy, cryotherapy and pulsed field ablation.[2] Radiofrequency energy continues to remain the widely practised mode of catheter ablation, although radiofrequency energy and cryotherapy have similar efficacy rates. Pulsed field ablation or electroporation has recently shown promising results in the first-in-human trials.[2]

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The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

LETTERS

Errors in electronic prescribing systems

I thank the authors for their insight into computerised prescribing in hospitals.[1] System-related prescribing errors present a conundrum. While the error is made by the clinician ordering the prescription, the user interface, layout design and workflow processes of electronic prescribing systems significantly impact upon the rate of errors. This has been illustrated by different error rates observed with different systems.[2,3]

Other problems can also cause clinical system-related prescribing errors:

1. Certain analgesics and antibiotics have two Pharmaceutical Benefits Scheme (PBS) item numbers listed with the same prescription drug descriptor. One is for use by medical or nurse practitioners, the other is for dental practitioners. Some systems compel the prescriber to choose one of the two similar prescribing options without differentiating which PBS number is for which prescriber.

2. Most guidelines recommend antibiotic doses to be taken with a predetermined interval (e.g. 6-hourly). However, antibiotic listings in some electronic prescribing systems are preset as number of times throughout the day (e.g. 4 times a day). While it does not significantly affect how oral medicines are taken, parenteral delivery timing under the National Inpatient Medication Chart system will be different for six-hourly versus four times a day. There are significant ramifications involving medicines that build up toxicity or require blood monitoring at a predetermined time of the day.

3. Electronic prescribing systems with decision-support modules incorporating accepted drug guidelines can assist prescribers to determine treatment without separately looking up the latest recommended resources. However, over-reliance by clinicians on software technicians for timely updates of these tools to incorporate latest guidelines opens up a minefield around the onus of responsibility for best-practice prescribing consistent with prevailing recommendations.

Electronic prescribing systems have great potential for reducing prescribing errors. However new errors, predominantly system-related prescribing errors, arising from system interface and content governance hinder efforts toward the goal of zero medication errors.

Shyan Goh
Orthopaedic surgeon, Meadowbrook, Qld

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Melissa Baysari and Magdalena Raban, authors of the article, comment:

These examples are highly relevant and illustrate the complexities associated with implementation of electronic prescribing systems. The last two examples also highlight the significant effort required to set up and maintain a safe electronic prescribing system. Ensuring that options available to prescribers for selection, including order sentences, reflect safe prescribing practice is not a trivial task. Neither is ensuring all guidelines, formulary items and decision-support functions remain up-to-date.

We disagree that a goal of 'zero medication errors' can be achieved. We join other researchers, clinicians and patient safety experts in advocating for a shift of focus away from zero errors and harm towards active risk management and organisational resilliance.[1,2] This will facilitate a reduction in medication errors but we cannot anticipate, detect and prevent every medication error. Human behaviour (and healthcare delivery) is too complex and unpredictable. We need electronic systems to support dynamic and flexible work in health care.

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Estimating renal function for patients in wheelchairs

After listening to the podcast and reading the article about drug dosing in chronic kidney disease,[1] I am still perplexed about the best way to estimate renal function (for drug-dosing purposes) for patients in wheelchairs. I have asked many colleagues without success.

I do many group home visits where the majority of patients are in wheelchairs and fed by PEG (percutaneous endoscopic gastrostomy), hence my question.

Penny Beirne
Pharmacist, Sydney

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1. Stefani M, Singer RF, Roberts DM. How to adjust drug doses in chronic kidney disease. Aust Prescr 2019;42:163-7. https://doi.org/10.18773/austprescr.2019.054

Darren Roberts, one of the authors of the article, comments:

The clinical issue raised here relates to disuse atrophy of the muscles which results in decreased creatinine production. It is therefore anticipated that a patient in a wheelchair with significant chronic kidney disease may have a serum creatinine concentration that is in the reference range. This means that routine laboratory reporting of the estimated glomerular filtration rate (eGFR) will incorrectly indicate that the patient has a 'normal' GFR.

Although there are limited data regarding this patient group, published studies have confirmed this hypothesis, and the limitations of simple approaches based on the serum creatinine concentration and either eGFR or estimated creatinine clearance (eCrCl). Both the eGFR[1,2,3] and eCrCl[1,3,4,5] commonly overestimated CrCl as measured on a 24-hour urine collection[1,2,4,5] or measured GFR (mGFR).[3,4] The actual CrCl measured on a 24-hour urine collection was approximately 70–80% lower than estimates using eGFR or eCrCl in two studies,[1,5] and even lower in patients who were quadriplegic.[5] In another study, the 24-hour urinary CrCl was on average 17 mL/minute higher than the corresponding mGFR.[3]

A few studies indicate that of the approaches which use a single blood sample, cystatin C-based methods are superior to creatinine-based methods.[4,6] However, these are not widely available.

Taken together, eGFR and eCrCl are more likely to be inaccurate in patients in wheelchairs, but interpatient variability precludes an adjustment factor being applied universally. Until more information is available, including data confirming the accuracy of cystatin C-based approaches, a CrCl based on 24-hour urine collection may be the simplest option, particularly in those with an indwelling urinary catheter. However, since this may also overestimate the actual GFR, then an mGFR should be considered if clinically indicated. Therapeutic drug monitoring should also be used when appropriate.

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New drugs

Fremanezumab

Approved indication: migraine

Ajovy (Teva)

pre-filled syringe containing 225 mg/1.5 mL

Patients with frequent migraine attacks can benefit from prophylactic drugs. Some patients will still be troubled by migraine despite prophylaxis. As the mechanisms of action of prophylactic drugs are not specific for migraine, there has been research into targeted drugs for prophylaxis. One target is the calcitonin gene-related peptide (CGRP). This peptide is involved in nociception and inflammatory processes. Like the previously approved galcanezumab, fremanezumab is a monoclonal antibody against CGRP.

The antibody has to be given by subcutaneous injection. It can be injected as 225 mg monthly or 675 mg (as three injections) every three months. When multiple injections are required, they should be given at different sites. After injection it takes about a week for the concentration of fremanezumab to reach its maximum. A steady state is achieved after approximately six months. The half-life is estimated to be 31 days.

Fremanezumab has been compared to placebo in patients with episodic and chronic migraine. The phase III trials evaluated both dose regimens over 12 weeks (see Table).[1,2] Patients with cardiovascular diseases were excluded.

The trial for preventing episodic migraine randomised 875 patients who had approximately nine days of

migraine in 28 days. Treatment with fremanezumab reduced the number of migraine days per month by 3.7 days with monthly injection and by 3.4 days with quarterly injection. The reduction in the placebo group was 2.2 days. The proportions of patients who had a 50% reduction in migraine days were 47.7% with monthly doses, 44.4% with a quarterly dose and 27.9% with placebo.[1]

The trial in chronic migraine enrolled 1130 patients who reported headaches on at least 15 days per month. On average, the participants had approximately 16 days of migraine every 28 days. At the end of the trial, monthly injections had reduced the number of headache days by 4.6 days and the number of migraine days by 5.0 days. With quarterly injection the reductions were 4.3 days for headache and 4.9 days for migraine. Both regimens were significantly better than the reductions of 2.5 days and 3.2 days seen in the placebo group. A reduction of at least 50% in the number of headache days was seen in 41% of the monthly group, 38% of the quarterly group and 18% of the placebo group.[2]

During the trials, adverse reactions to fremanezumab were more frequent than with placebo. In the patients with chronic migraine 47% developed injection-site reactions compared with 40% of the placebo group. These reactions consisted of pain, induration and erythema.[2] Some patients will develop antibodies to fremanezumab, but so far there have been few cases of neutralising antibodies or hypersensitivity reactions. Fremanezumab will cross the placenta, but caused no toxicity in animal studies.

Table   **Efficacy of fremanezumab for migraine prophylaxis**

Trial regimen (number of patients)	Number of days of migraine per month		Proportion of patients with at least a 50% reduction in days of migraine[1] or headache[2] per month
	Baseline	Change at 12 weeks	
Episodic migraine[1]			
Fremanezumab monthly (290)	8.9	–3.7	47.7%
Fremanezumab quarterly (291)	9.3	–3.4	44.4%
Placebo (294)	9.1	–2.2	27.9%
Chronic migraine[2]			
Fremanezumab monthly (379)	16.0	–5.0	41%
Fremanezumab quarterly (376)	16.2	–4.9	38%
Placebo (375)	16.4	–3.2	18%

The short-term trials show that fremanezumab is better than placebo, but the difference is small. A review of CGRP monoclonal antibodies by the US Institute for Clinical and Economic Review considered that the benefit was similar to other options for preventing migraine. It suggested that drugs such as fremanezumab may have a role if there has been an inadequate response to these other options.[3] A subsequent phase III trial has studied fremanezumab in 838 patients with migraine that had failed to respond to at least two, and up to four, prophylactic drugs. They were having an average of about 14 days of migraine a month. After 12 weeks, this had reduced by 4.1 days with monthly injections and 3.7 days with quarterly injection. Placebo resulted in a reduction of only 0.6 days. There was a reduction of at least half in the mean number of migraine days per month in 34% of the patients injecting fremanezumab compared with 9% of the placebo group.[4]

Despite the targeted approach, fremanezumab will benefit only a minority of patients with migraine. In the trial of patients who had not responded to other drugs, only 1% were free from migraine during treatment with monthly fremanezumab.[4] In patients with migraine who do respond, there is a need to see if this response is maintained in the longer term. Patients who used the quarterly regimen only received a single dose of fremanezumab in the 12–week trials.[1,2] The effectiveness of fremanezumab should be evaluated after 8–12 weeks to assess whether or not it should be continued.

T manufacturer provided the AusPAR and the product information

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

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

Risankizumab

Approved indication: psoriasis

Skyrizi (Abbvie)

pre-filled syringes containing 75 mg/0.83 mL

The skin inflammation seen in psoriasis is immune-mediated. This has led to immunomodulating drugs becoming part of treatment. While methotrexate has been used for many years, cytokine modulating drugs such as adalimumab, a tumour necrosis factor inhibitor, and ustekinumab, an inhibitor of interleukins 12 and 23, are more recently available. The systemic treatments are usually prescribed for patients with moderate–severe psoriasis.

Risankizumab is a monoclonal antibody that binds to interleukin 23 to prevent the cytokine binding to its receptor. As interleukin 23 is involved in peripheral inflammation, particularly T-cell responses, inhibiting it aims to reduce the skin lesions of psoriasis.

The drug is injected subcutaneously. To give the recommended dose of 150 mg, two injections are needed at different sites. Lower doses are not required in patients with hepatic or renal impairment. Risankizumab is catabolised and has an elimination half-life of 28 days.

A phase II randomised trial studied different doses of risankizumab in 126 patients with moderate–severe chronic plaque psoriasis. They were injected at the start of the trial and then, depending on the dose, at four weeks and 16 weeks. Another group of 40 patients received treatment with ustekinumab. The primary end point was a reduction of at least 90% on the Psoriasis Area Severity Index (PASI) at week 12 of the trial. This was achieved by 77% of the

patients injecting risankizumab 90 mg or 180 mg, compared with 40% of the ustekinumab group. The benefits of treatment were generally sustained for up to 20 weeks after the final injection.[1]

The phase III trials of risankizumab for moderate–severe plaque psoriasis used a dose of 150 mg given at baseline, at four weeks then every 12 weeks.[2,3] They also used a 90% reduction in the PASI as a main outcome for assessing efficacy.

The two UltIMMa trials allocated 997 patients (in a 3:1:1 ratio) to receive risankizumab, ustekinumab or placebo. At week 16 patients in the placebo group were switched to risankizumab. Most of the patients had previously received systemic treatments, including biological therapy. By 16 weeks the psoriasis was clear or almost clear in 84–88% of the risankizumab group with 75% achieving at least a 90% reduction in the PASI. This was a statistically superior outcome to ustekinumab and placebo. The PASI 90 was achieved by 42–48% of the ustekinumab group and 2–5% of the placebo group (see Table). Patients in the placebo group began to improve after they switched to risankizumab. By 52 weeks 78–85% of these patients had achieved a 90% reduction in the PASI. This was similar to the outcome (81–82%) for the patients who took risankizumab throughout the trial. Only 44–51% of the ustekinumab group achieved the same outcome.[2]

The IMMvent trial compared risankizumab with adalimumab in 605 patients. If the patients taking adalimumab had only had an intermediate response at 16 weeks, they were re-randomised to continue or switch to risankizumab. By week 16 there had been a reduction of at least 90% in the PASI score in 72% of the risankizumab group and 47% of the adalimumab group (see Table). The psoriasis was judged to be clear

Table   **Sixteen-week efficacy of risankizumab in moderate–severe psoriasis**

Trial	Treatments (number of patients)	Proportion of patients achieving primary outcomes	
		PASI 90*	**Clear or almost clear of psoriasis[†]**
UltIMMa-1[2]	Risankizumab (304)	75.3%	87.8%
	Ustekinumab (100)	42%	63%
	Placebo (102)	4.9%	7.8%
UltIMMa-2[2]	Risankizumab (294)	74.8%	83.7%
	Ustekinumab (99)	47.5%	61.6%
	Placebo (98)	2%	5.1%
IMMvent[3]	Risankizumab (301)	72%	84%
	Adalimumab (304)	47%	60%

* PASI Psoriasis Area and Severity Index. PASI 90 is a 90% or greater reduction in the index
[†] Based on a physician's global assessment score

or almost clear in 84% and 60%. In the 109 patients who were re-randomised from the adalimumab group, 66% achieved the PASI 90 at 44 weeks after being switched to risankizumab, compared with 21% of those who continued adalimumab.[3]

Immunomodulation can increase the risk of infection. While infections are more frequent than with placebo, the rate with risankizumab seems similar to the rate with ustekinumab[2] and adalimumab. For example, in the UltIMMa-1 trial infections occurred in 25% of the risankizumab group, 20% of the ustekinumab group and 17% of the placebo group. Tuberculosis should be excluded before treatment.

Injecting an antibody can induce an immune response. After 52 weeks, up to 14% of patients may develop neutralising antibodies against risankizumab.

Approximately 70% of the patients in the trials were men. There is little information about the drug in pregnancy and lactation.

Evidence is emerging that targeting the interleukins rather than tumour necrosis factor may have greater efficacy. The comparison with ustekinumab suggests that the higher efficacy of risankizumab could be related to its more selective inhibition of interleukin 23. It is currently unknown how risankizumab will compare with other inhibitors of interleukin 23, such as guselkumab, that have also been approved for psoriasis. Further research is needed to establish the role of risankizumab. For example, should treatment be continued long term or stopped and restarted? Long-term data should also reveal if there is any increase in malignancy or problems related to immunogenicity.

☒ manufacturer did not supply data

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

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

NEW DRUGS

Teduglutide

Approved indication: short bowel syndrome

Revestive (Shire)
vials containing 5 mg powder with diluent in
pre-filled syringe

Teduglutide is specifically indicated for patients with short bowel syndrome who are dependent on parenteral nutrition. It is an analogue of glucagon-like peptide-2 (GLP-2), which is a peptide hormone secreted by L cells in the distal bowel. Teduglutide activates GLP-2 receptors in the gut and causes release of insulin-like growth factor, nitric oxide and keratinocyte growth factor. This promotes repair and normal growth of the intestinal mucosa by increasing villi height and crypt depth.

The safety and efficacy of teduglutide (given subcutaneously) has been assessed in two main placebo-controlled trials. The studies enrolled people who had been receiving parenteral support for at least 12 months on at least three days a week. The aim of treatment was to decrease their dependence on parenteral support.

In a 24-week trial of 86 adults, those given teduglutide (0.05 mg/kg/day) were more likely to respond (>20% reduction in parenteral support from baseline) compared with those given a placebo (63% vs 30%). After 24 weeks of treatment, the mean reduction in parenteral support volume was 4.4 L/week with teduglutide compared to 2.3 L/week with placebo. Also, more people receiving teduglutide than placebo had at least a one-day reduction in weekly parenteral support (54% vs 23%).[1]

In patients who completed a two-year, open-label extension of the trial, 93% (28/30) continuing teduglutide responded compared to 55% (16/29) who changed from placebo to teduglutide.[2] After 30 months of daily teduglutide, 10 patients had been weaned off parenteral support.

In another 24-week trial, 83 people were randomised to daily teduglutide 0.05 mg/kg, 0.1 mg/kg or placebo.[3] The responder rate with the 0.05 mg/kg dose was significantly higher than with placebo (46% vs 6%, p=0.005). Although there were also more responders with the 0.1 mg/kg teduglutide dose compared to placebo, this effect did not reach statistical significance (25% vs 6%, p=0.17).[3]

In a 28-week extension of the study, 68% (17/25) of patients who continued the 0.05 mg/kg daily dose had responded. In people who discontinued teduglutide, weekly parenteral support volumes had to be increased after four weeks.[4]

After long-term treatment, almost half of the people receiving teduglutide 0.05 mg/kg had developed antibodies. However, these did not appear to affect the efficacy of the drug.

The common adverse events in the trial with teduglutide were abdominal pain (28%), nausea (26%), injection-site reactions (26%), abdominal distension (17%), stoma complication (16%), headache (16%) and vomiting (14%). These events were all less common with the placebo. Sleep disorders and anxiety were also more common with teduglutide. Other events included intestinal obstruction, biliary effects (cholecystitis, cholangitis, cholelithiasis), pancreatitis, pancreatic duct stenosis and pancreatic infection. Bilirubin, alkaline phosphatase, lipase and amylase should be assessed before teduglutide is started and during treatment.

There was one death in the trials that was considered to be related to teduglutide – this was from metastatic cancer from an adenocarcinoma found in the liver.[2] Teduglutide is contraindicated in people with a gastrointestinal malignancy, or a history of it.

Colonoscopy is recommended before starting teduglutide, after 1–2 years of treatment and then every five years. If detected, colorectal polyps should be removed before a patient starts teduglutide.

Teduglutide could potentially increase the absorption of oral medicines so care should be taken with concomitant drugs that require titration or have a narrow therapeutic index (e.g. benzodiazepines, opioids, digoxin and antihypertensive drugs). In vitro studies suggest that teduglutide does not affect cytochrome P450 enzymes. P-glycoprotein drug interactions are not predicted.

The recommended dose of teduglutide is 0.05 mg/kg a day. It should be given subcutaneously at alternating sites in the abdomen. It can also be given in the thigh or arm. Following injection, maximum plasma concentrations are reached after 3–5 hours. The half-life of teduglutide is 1.1 hours and the drug is thought to be eliminated by the kidneys. The dose should be halved in patients with moderate–severe renal impairment (creatinine clearance below 50 mL/min) and end-stage renal disease. Dose adjustment is not needed in mild–moderate liver impairment. The drug has not been tested in severe liver impairment.

Teduglutide seems to reduce the need for parenteral nutrition in people with short bowel syndrome and intestinal failure. However, continued teduglutide treatment is recommended in those who are able to be weaned off parenteral nutrition. Patients taking this drug need to be monitored for gastrointestinal cancer. The safety and efficacy of teduglutide has not been investigated in children.

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

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