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CONTENTS

ARTICLE

Medicines for long-term obesity management

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anti-obesity drugs, bupropion/naltrexone, hunger, liraglutide, orlistat, phentermine, semaglutide, topiramate, weight loss

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SUMMARY

Obesity is always genetic or epigenetic in origin in an obesogenic environment. Dietary therapy is required for weight loss.

Drugs to suppress hunger and increase satiety may assist while losing weight and are essential for most patients in the weight maintenance period. A combination of drugs may be needed.

A personalised approach must be used when selecting the appropriate weight loss drug for the patient. This considers possible contraindications, the method of administration and adverse effects, and includes discussing the cost of the treatment. Several drugs do not have an approved indication in Australia for weight loss.

Introduction

People with a body mass index above 30 kg/m^2 have obesity. There is strong evidence that obesity has a predominantly genetic[1] or epigenetic[2] basis. All other proposed causes of obesity, such as our modern lifestyle, gut bacteria and sleep deprivation, can modify weight but, on their own, cannot cause obesity. If a genetically thin person is put in an obesogenic environment, they will produce leptin which suppresses hunger. Although they will gain weight, they may not develop obesity.

Forced overfeeding studies from America have shown that, despite a group of individuals being overfed by the same amount, there is a range of weight gain. Those not gaining weight spontaneously increased their daily energy expenditure by around 2000 kilojoules.[3,4]

The genetic basis of obesity explains why the body defends weight so vigorously. Following even modest weight loss, there are long-lasting hormonal changes that lead to increased hunger and a reduction in energy expenditure.[5] This is why it may be helpful to consider using drugs to suppress hunger to assist with weight loss, depending on the diet being used to manage obesity. More importantly, these drugs are almost essential to help with maintaining the weight loss.

Drugs used in long-term management

There are several drugs for weight loss available in Australia (see Table),[6] however not all of them have an approved indication for obesity.

Phentermine

Phentermine is a sympathomimetic amine that acts on the brain to inhibit hunger.

Orlistat

Orlistat is an intestinal lipase inhibitor that slows fat digestion. It does not inhibit hunger, so it does not have a role in maintaining weight loss.

Liraglutide

Liraglutide is a glucagon-like peptide-1 (GLP-1) agonist with a hunger-suppressing action. It requires a daily injection with a starting dose of 0.6 mg. Liraglutide can cause nausea which settles after continued use. The dose can be slowly increased up to 3 mg daily, if required.

Semaglutide

Semaglutide 1 mg is approved in Australia for the treatment of type 2 diabetes. It is given as a weekly subcutaneous injection. Although GLP-1 agonists lower glucose in patients with diabetes, they do not cause hypoglycaemia in individuals who do not have diabetes. This is because GLP-1 requires elevated glucose concentrations to stimulate insulin secretion.

Low doses work very well in a subset of the population, but higher doses are needed by some. For these patients a 2.4 mg dose of semaglutide has been approved by the US Food and Drugs Administration (FDA) and is under consideration by the European authorities for the treatment of obesity. Compared to switching to placebo after 20 weeks, continued treatment with semaglutide can sustain weight loss.[7]

Bupropion with naltrexone

The combination of bupropion and naltrexone works by increasing activity in the melanocortin system of the hypothalamus. The starting dose is one tablet (bupropion 90 mg/naltrexone 8 mg) daily, gradually increasing to two tablets twice daily.

This article is peer-reviewed

Table **Drugs used in the maintenance of weight loss**

Drug	Doses available	Mode of action	Adverse effects	Contraindications	Efficacy (placebo subtracted losses)	Cost*
Phentermine	15, 30, 40 mg once daily	Sympathomimetic amine	Dry mouth Difficulty with sleeping Increased heart rate and blood pressure	Coronary artery disease Cardiac arrhythmias Use of antidepressant drug	6.4% weight loss	$145/month at highest dose
Orlistat	120 mg three times a day with meals	Intestinal lipase inhibitor	Steatorrhea	Pregnancy or breast feeding	4.1% weight loss	$92/month over-the-counter
Liraglutide 3 mg	0.6–3 mg once daily injection	Slows gastric emptying Suppresses hunger	Nausea Diarrhoea Constipation	History of pancreatitis	7.0% weight loss	$387/month at highest dose
Semaglutide	0.25–1 mg weekly injection	Slows gastric emptying Suppresses hunger	Nausea Diarrhoea Constipation	History of pancreatitis	8.6% weight loss	$132/month for 1 mg for patients without diabetes
Bupropion 90 mg/ naltrexone 8 mg	1–4 tablets daily	Increases melanocortin system activity	Nausea Constipation	Use of opioid analgesia Use of phentermine	6.3% weight loss	$242/month at highest dose
Topiramate	25–100 mg daily	Unknown	Paraesthesia Confusion Fetal abnormalities (cleft lip)	Glaucoma History of renal stones Pregnancy	7% weight loss	$22/month

* Costs in 2021

Topiramate

Topiramate is an antiepileptic drug. It has not been approved by the Therapeutic Goods Administration for the treatment of obesity in Australia because no one has applied to register it for treating obesity. However, topiramate in combination with phentermine was approved for the treatment of obesity by the FDA in 2012. Topiramate has frequent adverse effects that occur at higher doses. These include glaucoma, renal stones, paraesthesia and confusion. In addition, it has teratogenic effects on the developing embryo (cleft lip). The starting dose should be low (12.5–25 mg daily) for obesity management and the maximum dose should be 100 mg daily in two divided doses of 50 mg.

Considerations in drug selection

Drug therapy is part of the management of obesity. Clinical trials include diet and lifestyle interventions so patients still need to make lifestyle changes to benefit from drug treatment. When to start drug treatment depends on the diet being used for the management of obesity. For example, drugs may not be needed in ketogenic diets because ketones suppress hunger. The selection of the first drug to try is informed by the presence of any contraindications. A history of epilepsy excludes bupropion/naltrexone, pancreatitis excludes liraglutide and semaglutide, cardiac arrhythmia excludes phentermine, and glaucoma, renal stone disease and planning a pregnancy would exclude topiramate. The second consideration is cost and there is also a need to consider which drug would be the safest to use long term.

Efficacy and safety

A dose that works well with no adverse effects for one individual could cause very severe and intolerable adverse effects in another. All prescribers should warn their patients about this, then, by mutual agreement,

start one drug and be prepared to change to another if the first drug is not tolerated or is ineffective. Patients should be routinely monitored for adverse effects and the response to treatment.

Combination regimens

The body uses eight hormones to suppress hunger after a meal – cholecystokinin (CCK), peptide YY (PYY), glucagon-like peptide 1 (GLP-1), oxyntomodulin, uroguanilin, pancreatic polypeptide, amylin and insulin. It therefore makes sense that several drugs may be needed in combination to control hunger. If each medicine is used at a low dose, some of the adverse effects may be avoided. However, there is currently no evidence to support this approach.

Phentermine has been combined with topiramate and is available as a single capsule in the USA. In Australia, the two drugs can be prescribed separately.[8] Liraglutide or semaglutide could be combined with phentermine and topiramate or the bupropion/naltrexone combination. Phentermine should not be combined with bupropion/naltrexone. This is because bupropion has antidepressant effects and may increase cerebral serotonin. If that serotonin enters the blood stream, it normally would cause no harm, due to the avid uptake of serotonin by red blood cells. However, phentermine inhibits red cell uptake of serotonin so combining it with bupropion may increase circulating serotonin, which has been shown to cause heart valve fibrosis.

Treatment cost

Obesity rates are high in areas of low socioeconomic status. It is therefore important to consider the cost of the treatment when selecting a drug, a combination of drugs and the doses to be used. There is no subsidy for drugs that are approved for weight loss in Australia.

Duration of therapy

The hormone changes leading to increased hunger are very long lasting (at least six years, so probably life-long).[5] This should be taken into account when considering which drug should be chosen, in addition to dietary therapy, for the maintenance phase of weight loss.

Conclusion

Weight loss drugs are one part of the ongoing management of obesity. They are useful during the weight loss phase, but are essential in the maintenance phase. Patients need to be informed about the cost of these drugs, in addition to discussing efficacy and safety. <

Conflicts of interest: Joseph Proietto has been on the medical advisory boards for liraglutide, semaglutide 2.4 mg and bupropion/naltrexone. He has been involved in educational sessions for obesity management for both Novo Nordisk (liraglutide, semaglutide) and iNova (phentermine and bupropion/ naltrexone) for which he has received honoraria.

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Letters to the Editor

Drugs for pain management in frail older people

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While the article Pharmacological management of non-cancer pain in frail older people[1] accurately summarises the current literature and clinical guidelines, it provides little help to GPs struggling to provide appropriate pain management for frail older people. The bottom line is that the drugs recommended for use have very little benefit. We have seen a huge increase in the prescription of gabapentinoids by GPs attempting to avoid prescribing opioids, but there is little evidence of their effectiveness, and the associated adverse effects are significant. Doses of gabapentinoids tend to be subtherapeutic.

The advice to refer to geriatricians and pain specialists is fine in theory, but aside from issues of access, there are no magic bullets, and patients generally return to a drug not recommended in the guidelines.

It is little wonder that GPs resort to low-dose opioids, particularly in nursing home settings, where mobility and function are more likely to be limited, and the priority is the relief of suffering. In the absence of better alternatives, I do not think GPs are prescribing inappropriately in this setting.

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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

Statin doses after acute coronary syndrome

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Drs Eng-Frost and Chew address the diagnosis and management of acute coronary syndromes in their helpful review.[1] However, we question the need for the maximum tolerated statin dose in secondary prevention.

Significant toxicities are not always symptomatic and can be difficult to ascertain particularly in older patients or patients with comorbidities. Higher statin doses have not been shown to improve overall survival nor coronary mortality.[2,3] Safety and quality of life are important and toxicities increase with increasing drug doses.[4]

The greatest absolute risk reductions in mortality in randomised placebo-controlled clinical trials were seen with 40 mg of simvastatin or pravastatin in the 4S, HPS and LIPID studies.[3] Although some reductions in coronary events have been reported with higher statin doses, there is plateauing efficacy, as seen with all drugs at the top of their dose-response curves. This makes it likely that a greater reduction in coronary events will be achieved with statins in combination with other therapies such as antithrombotics, antihypertensive drugs, weight reduction and smoking cessation.

Specific target cholesterol concentrations have never been established in any appropriately designed randomised clinical trial. Epidemiology shows that reductions in coronary event rates plateau with lower cholesterol concentrations. There is no reduction, and in several analyses an increase, in mortality with total cholesterol concentrations below 5 mmol/L[5,6] (low-density lipoprotein cholesterols below 3.5 mmol/L).

In addition to plateauing efficacy, the failure of higher doses of statins to reduce mortality is likely to be related to the often non-plateauing increases in potentially serious toxicities, such as liver dysfunction,[3,7,8] diabetes,[9] cerebral haemorrhage[10] and renal impairment.[7,8] We suggest that for many patients it may be neither necessary nor prudent to increase doses, especially if the statin is used with other therapies known to reduce mortality.

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Joanne Eng-Frost and Derek Chew, the authors of the article, comment:

The recommendation that statins should be up-titrated to the highest tolerated doses is not solely intended to reduce mortality. It also aims to reduce the broader array of future coronary events, specifically recurrent myocardial infarction and revascularisation. There is a significant burden of recurrent events in patients who have symptomatic coronary artery disease.

The practice of encouraging the use of higher statin doses, to achieve lower concentrations of low-density lipoprotein in patients with symptomatic coronary artery disease to reduce recurrent cardiac events, is recommended in several guidelines. This provides greater benefit than the other therapies mentioned in the letter. However, clinical judgement and individualisation of therapy for each patient should always prevail when selecting statin doses.

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ARTICLE

The assessment of severe cutaneous adverse drug reactions

SUMMARY

Severe cutaneous adverse drug reactions include Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous pustulosis. These eruptions are a type of delayed hypersensitivity reaction and can be life-threatening.

The assessment of a severe cutaneous drug reaction requires a detailed clinical history and examination to identify the culprit drug and evaluate the allergy. Allopurinol, antibiotics and anticonvulsants are often implicated.

Patch testing and delayed intradermal testing can assist in determining if the reaction was allergic, however there is limited evidence about the sensitivity and specificity of skin testing in severe cutaneous adverse drug reactions. If the testing is non-conclusive or negative, it is recommended to avoid the suspected culprit drug and any structurally similar drug in future.

Any decision to reintroduce a drug should be made after considering the harm–benefit ratio. Caution is also needed if considering a possibly cross-reactive drug in a patient with a history of severe cutaneous adverse drug reactions.

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Keywords
acute generalised exanthematous pustulosis, adverse drug reactions, delayed hypersensitivity, drug eruptions, Stevens-Johnson syndrome

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Introduction

Skin eruptions can occur during drug treatment. They have a variety of causes including drug hypersensitivity. In allergic drug reactions, the immune system is triggered by a drug. These allergic reactions are unpredictable and not necessarily dependent on the dose.[1] In Australian primary care, 10% of the encounters are for an adverse drug event among which 11% are considered related to an allergic reaction.[2]

The immediate type of drug hypersensitivity reaction occurs soon after exposure to the drug. It is thought to be mediated by immunoglobulin E. In contrast, severe cutaneous adverse reactions are due to delayed drug hypersensitivity and are presumed to be T-cell mediated.[3] These immune-mediated reactions cause severe damage to the skin (Fig.) and internal organs, and are associated with significant acute and long-term morbidity and mortality. Allopurinol, antibiotics and anticonvulsants are often implicated.[4]

Clinical manifestations

Table 1 lists the severe cutaneous adverse reactions to drugs.[3] These include acute generalised exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (DRESS, also known as drug-induced hypersensitivity syndrome) and Stevens-Johnson syndrome. The Stevens-Johnson syndrome and toxic epidermal necrolysis are thought to be variants of the same condition. Mortality rates can reach 30–50%.[5] The distinction between Stevens-Johnson syndrome and toxic epidermal necrolysis is determined by the affected body surface area:

- 1–10% for Stevens-Johnson syndrome
- 10–30% for Stevens-Johnson syndrome or toxic epidermal necrolysis overlap
- >30% for toxic epidermal necrolysis.[3]

Several clinical manifestations should raise the suspicion of a severe cutaneous adverse reaction. These include dark-purple skin infiltration, facial swelling, skin peeling and blistering, mucosal involvement, adenopathy, fever and haematological and biochemical laboratory abnormalities. A presence of any of these should warrant urgent hospital referral.

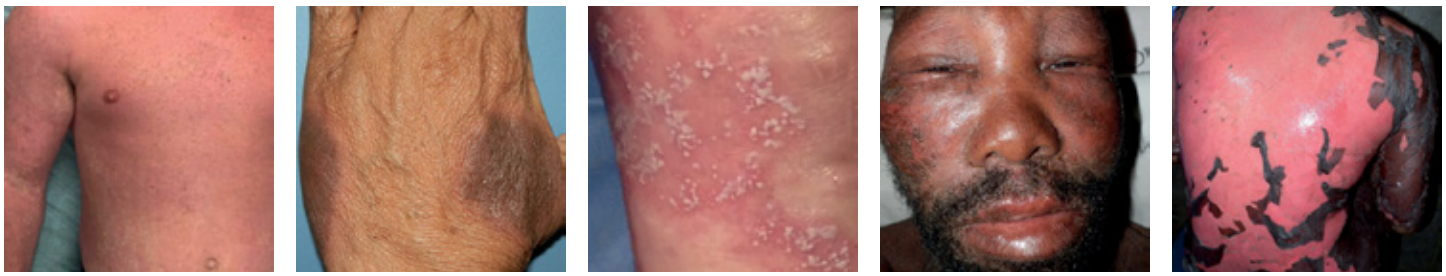
An adverse event that involves a drug should be reported to the Australian Therapeutic Goods Administration.

Other drug eruptions

The most common benign cutaneous reaction to drugs is the maculopapular exanthema or morbilliform drug eruption. This is characterised by maculopapular red skin lesions that can become widespread and confluent. There may be pruritus and mild eosinophilia.[3]

The fixed-drug eruption is a reaction characterised by well-defined, red–dark, burning or itchy lesions. These lesions may reappear in the same areas on

Fig. **Clinical representations of patients with severe cutaneous adverse reactions**



Adapted, with permission from Elsevier, from reference 13

Table 1 **Diagnostic tests and scoring algorithms for assessing delayed drug hypersensitivity reactions**

	Acute generalised exanthematous pustulosis	Drug reaction with eosinophilia and systemic symptoms	Stevens-Johnson syndrome/ toxic epidermal necrolysis
Clinical manifestations	Non-follicular sterile pustular rash over widespread erythema, fever and laboratory abnormalities*	Erythematous urticaria-like or violaceous skin eruption, facial and extremity oedema, lymphadenopathy, fever, laboratory abnormalities* and internal organ involvement	Skin necrosis, skin detachment and blistering of the mucous membranes accompanied by serious systemic manifestations
Commonly implicated drugs[3]	Antibiotics (penicillins, cephalosporins) Antimycotics Other (diltiazem, antifungals, analgesics)	Anticonvulsants Antibiotics (sulfonamides, vancomycin, minocycline) Allopurinol	Allopurinol Anticonvulsants Antibacterial sulfonamides Nevirapine NSAIDs Antituberculosis drugs
Scoring algorithms			
Disease likelihood	AGEP validation score	RegiSCAR score	n/a
Drug causality	Naranjo score	Naranjo score	ALDEN score Naranjo score
Mortality prediction			SCORTEN
Diagnostic tests			
Patch testing	Indicated	Indicated	Indicated
Delayed intradermal testing	Indicated	Indicated	NOT indicated
Oral challenge	NOT indicated	NOT indicated	NOT indicated

* Laboratory abnormalities refer to biochemical abnormalities such as increased concentrations of creatinine and liver enzymes (aspartate aminotransferase, alanine aminotransferase) or haematological abnormalities such as eosinophilia and neutrophilia.

NSAIDs non-steroidal anti-inflammatory drugs
AGEP acute generalised exanthematous pustulosis
RegiSCAR European registry of severe cutaneous adverse reactions
n/a not applicable
Naranjo adverse drug reaction probability scale
ALDEN algorithm of drug causality for epidermal necrolysis
SCORTEN score of toxic epidermal necrosis

re-exposure to the drug.[5] In a generalised bullous fixed-drug eruption there are sharply defined bullae at the same site following recurrent administration of the offending drug.[6]

Another drug eruption is symmetrical drug-related intertriginous and flexural exanthema. This is a well-demarcated macular eruption involving the flexural or intertriginous folds, and inguinal and perigenital as well as the gluteal and perianal areas.[7]

While technically not severe cutaneous adverse reactions, drug-induced liver injury and acute interstitial nephritis are examples of possibly severe single-organ diseases that can have pruritic skin eruptions.

Another multisystem disease related to drug exposure is the abacavir hypersensitivity syndrome. This is characterised by skin eruption, fever and gastrointestinal symptoms usually in the first weeks of therapy.[8,9]

Diagnostic tools

Some tools have been developed to help establish the likelihood of a particular reaction (Table 1). Examples include tools for the diagnosis of acute generalised exanthematous pustulosis,[10] DRESS[11] and Stevens-Johnson syndrome or toxic epidermal necrolysis.[12]

In some cases of atypical skin lesions, a skin biopsy could be performed. However, there are no definitive histological criteria for the diagnosis of drug-induced eruptions and a skin biopsy might not exclude alternative causes for the eruption. Biopsy is supportive but not definitive.

Investigating drug causality

As patients are often taking numerous drugs, evaluating drug causality in severe cutaneous adverse reactions can be challenging.[4,5,13-15] The initial assessment includes constructing a drug timeline from the patient's history and a detailed review of any drugs started in the 6–8 weeks before the reaction occurred. Generally, drugs started eight weeks before the skin eruption are not implicated. Common offenders include:

- antibiotics and antifungals for acute generalised exanthematous pustulosis
- anticonvulsants for DRESS
- allopurinol for Stevens-Johnson syndrome or DRESS (Table 1).[3]

Some of the severe cutaneous adverse reactions present with constitutional symptoms, so one must keep in mind that some of the drugs given to treat these early symptoms might be incorrectly considered to have caused the eruption. Using validated drug causality tools (Table 1) such as the Naranjo score[16] can help to minimise this error. This simple and widely used scale is reserved for the evaluation of adverse drug reactions.[17] A Naranjo score of 4–5 is likely to indicate drug causality.

These tools help to categorise the most likely causal drug, considering the type of drug, the timing and possible alternative causes.[18] If the repeated administration of a suspected drug has caused no symptoms, that drug may be excluded as a possible offender. Similarly, recurrent symptoms that present following the administration of the same drug would increase the likelihood that it caused the reaction. If similar signs and symptoms have occurred in the absence of any medicine, a non-drug-related condition should be considered in the differential diagnosis.

Some specialised centres are developing new laboratory tools, which examine cytokine production from isolated patient T cells. These aim to help evaluate drug causality, however their use is currently reserved for research purposes.[19-21]

Drug allergy investigations

Following complete resolution of the acute reaction, various investigations are available in specialised centres. These are generally performed at least six weeks after the complete resolution of the acute disease or after stopping immunosuppressive treatment.[19,22]

Patch testing involves applying a diluted sterile concentration of the implicated drug in a soluble medium under occlusion on the patient's skin, to see if the initial reaction is reproduced in that small testing area. This is a quick and safe investigational method and is clinically relevant if the result is conclusive. A negative patch test does not exclude the drug as a possible cause.[23] For severe delayed immune-mediated reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, patch testing should be delayed for six months after the resolution of the skin reaction.[24]

Intradermal testing with delayed reading (48–72 hours) can be done with various non-irritating concentrations of sterile commercially manufactured preparations.[22] These are injected into the forearm. Like patch testing, intradermal testing should be performed at least four to six weeks after an acute reaction. The ability of delayed intradermal testing to detect true cases of allergy varies. Its sensitivity for antimicrobials ranges from 6.6–36.3% for cases of maculopapular exanthema to 64–100% for DRESS.[25] In our Australian experience, intradermal testing has identified the causative drug in 46–56%, particularly for cases of severe maculopapular exanthema and DRESS.[19,26]

Safety considerations and the low described sensitivity and specificity of intradermal testing and patch testing limit their use in the management of severe cutaneous adverse reactions.[22,27,28] Considering the limited number of diagnostic tools for the assessment of these very severe conditions, skin testing is still considered an essential clinical tool for providing guidance to clinicians. Conclusive results on skin testing will help to identify alternative drugs for patients who have multiple allergies.

The gold standard for drug allergy assessment is drug rechallenge. Depending on the availability of the implicated drug, a rechallenge can be performed with oral, intravenous or intramuscular doses. However, a rechallenge is not without risk and there are often other drug alternatives. The majority of local and international guidelines advise against a drug rechallenge in patients who have had severe cutaneous adverse reactions.

Cross-reactivity

Cross-reactivity is when an individual, previously exposed and allergic to a drug, is exposed to a structurally similar drug, and the immune system recognises the shared chemical structure resulting in an allergic reaction.

The majority of the data on cross-reactivity come from immediate rather than delayed hypersensitivity.

When a patient is allergic to a drug and the alternatives are limited or associated with adverse drug reactions, allergy investigations are suggested. Skin testing can be performed with the implicated and cross-reactive drugs. If skin testing is positive in the setting of a severe systemic reaction, the tested and structurally similar drugs must be avoided. A similar approach is recommended in the setting of a non-conclusive test and there must always be a consideration of the harm–benefit ratio.

Antibiotics

The most common example of cross-reactivity is among the penicillin family of antibiotics. However, the label of penicillin allergy may be incorrect.[29] According to studies on delayed hypersensitivity reactions, among a cohort of patients with positive patch testing or intradermal testing to at least one penicillin reagent, none of the patients reacted to carbapenems.[30] Following specialist consultation, carbapenems could be considered for a patient with a history of a severe cutaneous adverse reaction to penicillin. If the initial reaction was to an aminopenicillin, the recommendation is to avoid all aminocephalosporins sharing a similar side chain, such as cefalexin and cefaclor.[25] Following an assessment of the allergy, these patients could be able to tolerate other cephalosporins.[31,32] Cefazolin has no common side chains with other molecules and is regularly tolerated by patients with a penicillin or cephalosporin allergy – however, specific data regarding severe cutaneous adverse reactions are lacking.

In patients labelled allergic to sulphonamides such as the trimethoprim and sulfamethoxazole combination, studies have reported that there is no cross-reactivity between antibacterial (e.g. sulfasalazine and sulfamethoxazole) and non-antibacterial sulphonamides (e.g. acetazolamide, furosemide (frusemide), celecoxib, thiazide diuretics, sumatriptan, sotalol, probenacid).[25] This lack of cross-reactivity has also been reported for cases of severe cutaneous adverse reactions.[33] However, there seems to be cross-reactivity between dapsone and trimethoprim/sulfamethoxazole and caution is advised.[34,35]

Cross-reactivity has also been reported among the drugs belonging to the families of macrolides, tetracyclines, aminoglycosides, quinolones, glycopeptides and nitroimidazoles.[25]

Allopurinol

Allopurinol can cause a maculopapular drug eruption and severe cutaneous adverse reactions such as DRESS, Stevens-Johnson syndrome and toxic epidermal necrolysis with an overall incidence of 2%.[36] The median time of onset is three weeks, but some reactions have been reported several years after starting treatment.[37] In patients who have an indication for urate-lowering treatment (e.g. gout, hyperuricaemia and tumour lysis syndrome) and who have had a severe reaction to allopurinol, alternative drugs should be considered. Some studies have described desensitisation regimens and the harms and benefits of these should be discussed with an allergy specialist.[38]

Anticonvulsants

Patients who have reacted to aromatic antiepileptic drugs, such as carbamazepine, oxcarbazepine, phenytoin, phenobarbital, lamotrigine, felbamate and zonisamide, should avoid all the drugs of this specific family. However, there is evidence that these patients will tolerate valproic acid and structurally distinctive anticonvulsants, such as benzodiazepines (e.g. clobazam, clonazepam) and gabapentin.[39]

Genetic screening

There are specific genetic associations between human leukocyte antigen (HLA) alleles and severe cutaneous adverse reactions. These discoveries have increased the understanding of the immune mechanisms of delayed hypersensitivity reactions and enabled the development of screening guidelines and specific programs (Table 2).[13,40,41]

Table 2 **Genetic screening in delayed immune-mediated adverse drug reactions**

Drug	Severe cutaneous adverse reactions	Human leukocyte antigens	Ethnicity†	Screening
Abacavir	Hypersensitivity syndrome[40,41]	B*57:01	5–8% Caucasian <1% African/Asian 2.5% African American	Routine screening HIV-positive patients
Allopurinol	Stevens-Johnson syndrome/ toxic epidermal necrolysis DRESS	B*58:01	9–11% Han Chinese 1–6% European ancestry	Selective screening. Mostly considered for Han Chinese as data are incomplete for African and European ancestry
Dapsone	DRESS	B*13:01	2–20% Chinese 28% Papuans/ Australian Aboriginal people 0.019% European 1.5% Japanese <2% African and African American	Routine screening programs in South-East Asian countries where leprosy is prevalent
Carbamazepine	Stevens-Johnson syndrome/ toxic epidermal necrolysis	B*15:02	10–15% Han Chinese <1% Koreans, Japanese <0.1% European ancestry	Routine in South-East Asian countries
Vancomycin	DRESS	A*32:01	4% African American <1.5% South-East Asian	There is currently no clear role

† The percentage refers to the carriage rate of the HLA allele.
DRESS drug reaction with eosinophilia and systemic symptoms
Adapted from references 13 and 39

HLA alleles have a different prevalence in different populations, providing a possible explanation for why some groups are more prone to severe cutaneous adverse reactions.[39] For example, in people with HIV, the risk of abacavir hypersensitivity can be reduced by screening for HLA-B*57:01 before prescribing.[40] Some South-East Asian countries routinely test before treatment with dapsone or carbamazepine in order to prevent DRESS (HLA-B*58:01), Stevens-Johnson syndrome and toxic epidermal necrolysis (HLA-B*15:02) (Table 2). Allopurinol has been associated with DRESS, Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese people with the HLA-B*58:01 allele. At present, there is no clear role for predictive HLA screening in this population and testing is reserved for patients who have had a hypersensitivity reaction. However, the American College of Rheumatology has recommended preventive screening for patients of Korean ethnicity with chronic kidney disease stage 3 or worse and patients of Han Chinese or Thai ethnicity irrespective of renal function before starting allopurinol.[42] If more genetic associations are found to be associated with severe cutaneous adverse reactions, HLA testing may become increasingly useful for screening and diagnosis.

Conclusion

A detailed history is essential if a skin eruption is possibly drug related. Identifying the drugs implicated in severe cutaneous adverse reactions can be aided by the use of drug causality assessment tools. Skin testing can assess the allergy. In future, genetic testing may help to avoid these potentially life-threatening reactions. ≺

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FURTHER READING

DermNet NZ. [Free resource all about the skin, supported by New Zealand Dermatological Society Incorporated] https://dermnetnz.org [cited 2022 Mar 1]

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ARTICLE

Antidepressants in adolescence

SUMMARY

In adolescence, antidepressants are second-line treatment options after psychological therapy for anxiety and obsessive compulsive disorder. They may be first- or second-line options for severe cases of major depressive disorder.

The response to antidepressant treatment is generally good for anxiety and obsessive compulsive disorder, but is less convincing for major depressive disorder. Adolescents who do not respond to an adequate trial of one antidepressant should be referred for a psychiatric opinion.

Patients must be monitored for rare but serious adverse effects. These include suicide-related behaviours, switching to mania, and serotonin syndrome.

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Keywords
adolescent, antidepressive drugs, anxiety disorders, depressive disorder, obsessive compulsive disorder

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Introduction

The antidepressants approved for use in Australia are the selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and a miscellaneous group that includes drugs such as agomelatine and mirtazapine. Other drugs such as quetiapine and lurasidone, may be used to manage depressive symptoms under special circumstances. For adolescents (aged 12–17 years) the approval of the Therapeutic Goods Administration is limited to the SSRIs fluvoxamine and sertraline for obsessive compulsive disorder, and the tricyclic antidepressants amitriptyline and imipramine for enuresis.[1] All other prescribing is 'off label'.

The rate of antidepressant prescribing to Australian adolescents rose steadily between 2013 and 2019, with SSRIs being by far the most commonly prescribed class.[1] General practitioners accounted for 55% of the antidepressant prescribing to 12–14 year olds, increasing to 78% for 15–17 year olds.[1]

Potential indications in adolescence for antidepressant drugs include enuresis, attention deficit hyperactivity disorder, anxiety, obsessive compulsive disorder, selective mutism, anxiety or obsessionality associated with autism and intellectual disability, aggression, bulimia and major depressive disorder. General practitioners are most likely to consider starting an antidepressant for major depressive disorder or an anxiety disorder,[2] but they may be asked to provide maintenance prescriptions for treatment started by a paediatrician or psychiatrist.

Evidence of efficacy

For adolescents, more antidepressant drugs are effective for anxiety disorders and obsessive compulsive disorder than they are for major depressive disorder. Reviews of efficacy and safety have increased in sophistication with time, but the overall conclusions have not altered much in the past two decades. Key findings of a meta-review[3] are summarised in the Table.

There are limitations in the current evidence. Relative to studies in adults, there are fewer trials in children and adolescents, the sample sizes are small, and study quality is low. The evidence is almost exclusively about first-line treatment in the acute phase of illness. There is little evidence to guide maintenance treatment, or the strategies to use if first-line treatment is ineffective. Unfortunately, most treatment trials combine data from children and adolescents, which is then reflected in the scope of systematic reviews. It is plausible that, as adolescents approach adulthood, their pattern of response to drugs also begins to approximate that of adults. As such, GPs must use judgement in interpreting and communicating efficacy data derived from paediatric populations when applied to older adolescents.

Adverse effects

Common, generally mild adverse effects include sleep disturbance, tremor, sweating, gastrointestinal discomfort and sexual dysfunction. Abruptly stopping SSRIs may lead to a discontinuation syndrome, characterised by malaise and other flu-like symptoms. Antidepressants can also cause behavioural activation, characterised by irritability, agitation and anxiety. Important but rare adverse reactions are the induction of manic symptoms (known as 'switching'), and serotonin syndrome.

Suicidal behaviour

A concern is the small potential for antidepressants to trigger suicide-related behaviours in some adolescent patients. No positive association has been found between antidepressant prescriptions

and suicide deaths. Suicide-related behaviours refer to self-harm and suicidal thoughts, which are sometimes associated with stimulation or agitation (known as 'activation syndrome'). These behaviours occur in the weeks after starting antidepressant drugs in about 4% of adolescents, which is double the rate seen in those given a placebo.[4] Suicide-related behaviours are most likely to occur with the SNRI venlafaxine, and less likely to occur with SSRIs such as fluoxetine and escitalopram.[5] An analysis of safety data from paediatric antidepressant trials found the risk for developing suicide-related behaviours was significantly elevated in patients with major depressive disorder, but not in other mental disorders.[4] SSRIs and SNRIs are safer in overdose than the older tricyclic antidepressants and MAOIs.

Anxiety and obsessive compulsive disorder

Neither anxiety nor obsessive compulsive disorder interferes with the capacity to engage with treatment. Provided that it is accessible, psychological therapy is the treatment of first choice for both disorders because it avoids exposure to adverse effects. Pharmacotherapy is reserved for patients who do not respond to psychological therapy, or for some reason are unable to engage with therapy.

For anxiety, there is stronger evidence supporting the use of fluvoxamine than the other drugs listed in the Table. Fluvoxamine is relatively sedating which can be useful for a patient who is experiencing disturbed sleep.

In obsessive compulsive disorder, fluoxetine is the first-choice drug because of its favourable safety profile relative to other drugs (Table). Clomipramine (a tricyclic antidepressant with a strong serotonergic action) is reserved for treatment-refractory cases.

Initial and maximum doses are summarised in the Table. Try the initial dose for two weeks. If the drug is tolerated, titrate the dose upward in increments of half the initial dose every two weeks. When there is an inadequate response to six weeks of treatment at the highest tolerated dose, seek the opinion of a psychiatrist. If treatment is effective, it may need to be indefinite, as anxiety and obsessive compulsive disorder are chronic relapsing conditions.

Table **Drugs with established short-term efficacy for selected mental disorders in adolescents[3] and suggested doses**

Indication	Effective drug
Anxiety disorder (including generalised anxiety, mixed anxiety, social anxiety, separation anxiety, school phobia and elective mutism)	Fluvoxamine initial dose 25 mg/day maximum dose 300 mg/day (doses over 50 mg should be divided) Sertraline initial dose 50 mg/day maximum dose 200 mg/day Paroxetine initial dose 20 mg/day maximum dose 60 mg/day Fluoxetine initial dose 20 mg/day maximum dose 80 mg/day
Obsessive compulsive disorder	Fluoxetine initial dose 20 mg/day maximum dose 80 mg/day Sertraline initial dose 50 mg/day maximum dose 200 mg/day Paroxetine initial dose 20 mg/day maximum dose 60 mg/day Clomipramine initial dose 25 mg/day maximum dose 250 mg/day
Major depressive disorder	Fluoxetine initial dose 20 mg/day maximum dose 80 mg/day

Depression

Adolescents with a major depressive disorder do not have a particularly good response to either psychological therapy or pharmacotherapy. The characteristics of the illness compromise engagement with psychological therapy ('I'm too tired, I'm not worthy of treatment, I can't concentrate, what's the point, I'm soon going to be dead anyway'). Adherence to pharmacotherapy may also be poor. Adolescents who present with depressive symptoms may not have a primary mood disorder. The depressed (or more often dysphoric) mood may be a feature of borderline personality disorder, eating disorder, gender identity disturbance, conduct disorder, or a reaction to traumatic experiences. With the exception of bulimia, none of these conditions is likely to respond to antidepressant therapy. Depressed adolescents with complex or ambiguous presentations should be referred for a psychiatric opinion.

For adolescents with a mild case of major depressive disorder (symptomatic but with no or minimal functional impairment), supportive care and psycho-education is the first-line management. Attention to their sleep routine, diet and exercise may be sufficient to resolve symptoms. If not, these patients should be referred for psychological therapy.

The approach to moderate to severe cases of major depressive disorder (significant functional impairment or suicidality) in adolescence is less clear-cut. UK

guidelines recommend psychological therapy first.[6] US guidelines recommend starting with either psychological therapy or pharmacotherapy, then switching to or adding the other modality if there has been an inadequate response.[7] Evidence shows that the response to psychological therapy and fluoxetine is similar. The time to response is shorter with fluoxetine than with psychological therapy, but suicide-related behaviours are more common.[8] Fluoxetine is the treatment of first choice when a rapid remission is a high priority. This is important because the longer the episode of major depressive disorder, the greater the impact on academic and social functioning. If safety is the top priority, psychological therapy is the treatment of choice. This is relevant when a young person with major depressive disorder has prominent suicide ideation, or has engaged in self-harm. In contrast to studies in adults, combined therapy is not superior to psychological or pharmacological monotherapy for first-line treatment of adolescents with major depressive disorder.[8]

While most responders to fluoxetine will start to improve within a few weeks of starting treatment, some may take several months. In the initial phase, the adolescent should be reviewed at least every two weeks. Emphasis in the early weeks will be on the detection of serious adverse effects such as behavioural activation, and emergent or increasing suicidality. The adolescent is typically the last person to notice improvement, so corroborative information from family or teachers can be very helpful. Clinicians should focus on functional improvement (objective data) over subjective reports of mood. Greater engagement in school and social activities and an improvement in total sleep time are useful markers of improvement.

If after 12 weeks there has been an inadequate response to any first-line treatment, seek the opinion of a psychiatrist. The recommended interval for review is longer than for anxiety disorders, because major depressive disorder is typically slower to respond to treatment. If there are severe adverse effects, refer to an emergency service.

For an adolescent who has responded to fluoxetine, the drug should be continued for a further 12 months to prevent relapse. Discuss this with the adolescent at the consenting phase, so there are no later misunderstandings about the need to continue therapy. Adolescents are likely to stop treatment if there are adverse effects,[9] so be pro-active in surveying symptoms at each review.

Stopping treatment

When withdrawing antidepressant treatment, taper the dose in two or more steps over one to two weeks. If a discontinuation syndrome emerges, raise the dose to stop the symptoms and then resume withdrawal at a much slower rate.

Conclusion

Antidepressants are an effective second-line treatment for adolescents with anxiety or obsessive compulsive disorder who have not responded to, or not engaged with, psychological therapy. Antidepressants also have a first- or second-line role in the treatment of adolescents with moderate to severe major depressive disorder.

Adolescents treated with antidepressants must be monitored for the emergence of rare but serious adverse effects, such as suicide-related behaviours, switching to mania and serotonin syndrome. If effective and well tolerated, the antidepressant drug should be continued for 12 months for major depressive disorder and indefinitely for anxiety and obsessive compulsive disorder. <

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FURTHER READING

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Troponins in myocardial infarction and injury

SUMMARY

Troponins are proteins that are integral components of the contractile mechanism of muscle, including cardiac muscle. Cardiac troponins I and T can be detected in the blood of most people after puberty, at concentrations reflecting cardiac mass, sex and age.

Current laboratory assays are approximately 1000 times more sensitive than those used previously. They also have higher sensitivity than point-of-care assays.

The measurement of cardiac troponins is used primarily to assist in the diagnosis or exclusion of myocardial injury. Serial tests in acute coronary syndrome are guided by the Universal Definition of Myocardial Infarction.

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Keywords
acute coronary syndromes, myocardial infarction, cardiac troponins, point-of-care testing

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Introduction

Troponins are proteins that regulate muscle contraction.[1] In the myocardium the subunits are cardiac troponin I (cTnI), cardiac troponin T (cTnT) and cardiac troponin C. All three are integral components of the contractile mechanism of cardiac muscle (see Fig. 1). They have separate genes, which differentiate them from skeletal muscle troponin.

Immunoassays have been developed for both cTnI and cTnT and either of these troponins can be used in the investigation of possible myocardial injury or infarction. As cardiac troponins are specific for myocardial tissue, they have now replaced creatine kinase-MB for investigating possible myocardial injury.

Troponin assays

Early assays for cTnI and cTnT were relatively insensitive. Only high concentrations could be detected in the circulation. This led to the concept that troponin release from the myocardium only occurred after significant ischaemic damage. The detection of troponins in the blood became almost synonymous with acute coronary syndrome. However, newer assays are approximately 1000-fold more sensitive so they can detect troponins in people without ischaemia. Low concentrations can be detected in the circulation in healthy people throughout life, and almost all children from near puberty have detectable cTnI in their blood.[2] Plasma concentrations are lower in females than males because of their smaller cardiac mass. Many causes of myocardial damage other than ischaemia are associated with troponin elevations in the circulation and high concentrations can occur in marathon runners (Box 1).[3-6] The diagnosis or exclusion of acute coronary syndrome remains the most common and important reason for measuring troponins.

The half-life of cardiac troponins

The actual half-life of both cTnI and cTnT is short – approximately two hours in plasma.[7] However, because of continued leaching of troponin from necrotic myocardium, the apparent half-life is of the order of 24 hours with cTnT slightly longer.[8]

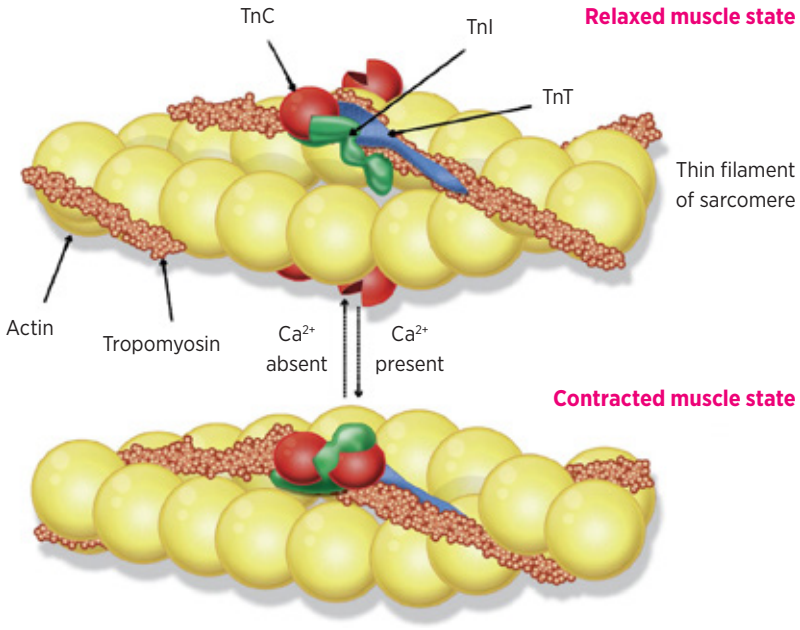
What is measured

For technical reasons (namely the sample volume used) cTnI assays measure to lower concentrations than cTnT. However, in the diagnosis of myocardial infarction there is little difference between cTnT and cTnI. An exception is in patients undergoing haemodialysis, where cTnT is marginally superior in identifying those at risk of cardiac death.[9] Whether a particular laboratory measures cTnI or cTnT will depend on the analytical equipment it has chosen. Only one company offers cTnT, whereas multiple platforms offer cTnI assays.

All troponin assays offered in major hospital and pathology laboratories in Australia are high-sensitivity assays. However, the concentrations measured by different assays are not interchangeable. The equipment manufacturers have not benchmarked their particular antibodies against each other and there has been no harmonisation of the immunoassays. This means that the reference intervals reported by different laboratories will vary.

Some small laboratories and geographically more remote locations are unable to support significant large instrumentation and rely on point-of-care testing for troponin. While these tests are generally robust, their limits of detection are higher. For example, the limit of detection for cTnI may be 20 nanogram/L compared with 2 nanogram/L for a high-sensitivity assay.[10] For measuring cTnT using

Fig. 1 **Cardiac muscle**



Cardiac muscle showing location of cardiac troponin I (TnI), cardiac troponin T (TnT), and cardiac troponin C (TnC) in relation to actin and tropomyosin.

Ca^{2+} Calcium ions
Source: Adapted, with permission from Elsevier, from reference 1.

Box 1 **Examples of causes of elevated cardiac troponin[3]**

Cardiac ischaemia

Acute coronary syndrome/Type 1 myocardial infarction

Heart failure

Type II myocardial infarction. Supply and demand mismatch e.g. hypotension including intraoperative, cardiac dysrhythmias and significant blood loss

Cardiac inflammatory and infiltrative diseases (various aetiologies)

Myocarditis

Respiratory

Pulmonary embolism

Adult respiratory distress syndrome, respiratory failure

End-stage renal disease

Infections

Viruses – various, including COVID-19

Sepsis

Toxicity

Carbon monoxide poisoning

Drugs e.g. clozapine, chemotherapy[4]

Envenomation e.g. jellyfish and snake[5,6]

Miscellaneous

Blunt force trauma e.g. motor vehicle accident

Endurance sports

the point-of-care testing, the limit of detection is 100 nanogram/L versus 5 nanogram/L for a high-sensitivity assay.[11] As significant myocardial injury can occur with troponin concentrations below the limits of detection, some cases of concern may be missed by point-of-care tests. High-sensitivity point-of-care assays are in development, but are not currently in use in Australia.

Troponins and acute myocardial infarction

The Fourth Universal Definition of Myocardial Infarction (Box 2) requires a rise and fall in troponin concentration with at least one result above the 99th percentile, and objective evidence of myocardial ischaemia.[12] The most common form of acute coronary syndrome seen in the emergency department is type 1 myocardial infarction. This is caused by the rupture of an atheromatous plaque, thrombi formation and embolisation causing coronary artery obstruction and necrosis. Type 2 myocardial infarction occurs when oxygen delivery to the myocardium is inadequate.[13] Other types of myocardial infarction are rare.

The universal definition uses the 99th percentile of troponin concentrations in a healthy population. This is challenging as defining a healthy population is difficult. Detailed examination shows many apparently healthy people have significant sub-clinical cardiac disease. Depending on how carefully a population is chosen, the reported 99th percentile can vary markedly.[14] In addition, both sex and age (increase with age) are important contributors to population data sets even in a carefully selected population.[15] In Australia the 99th percentiles (depending on the assay used) are:

- cTnI males 26 nanogram/L, females 16 nanogram/L
- cTnT males 15.5 nanogram/L, females 9 nanogram/L.

Box 2 **Fourth universal definition of myocardial injury and myocardial infarction[12]**

Myocardial injury

Troponin concentration above the 99th percentile

Myocardial infarction (type 1)

A rise and fall in troponin concentration with at least one value above the 99th percentile

Symptoms of myocardial ischaemia

New ischaemic ECG changes

Development of pathological Q waves

Imaging evidence of loss of viable myocardium or new regional wall abnormality

The universal definition introduced the 99th percentile to assist the recognition of clinically important elevations of cardiac troponin. However, it is important to recognise that with the very small biological variation of both cTnT and cTnI in healthy individuals these concentrations may fall well below the 99th percentile. A pathologically significant troponin release can therefore occur and still be below the 99th percentile in some individuals.[16]

Interpretation of results

The single major use of troponin assays is for the diagnosis or exclusion of acute myocardial infarction in the emergency department. Only 5–10% of people who are assessed are ultimately proven to have a myocardial infarction.[17] Troponin is therefore mainly used in the emergency department as a 'rule-out' test. A low troponin concentration at presentation with small changes over a period of 1–3 hours provides the best rule-out rates.[18] Sex-specific cutpoints are recommended for use by both the Fourth Universal Definition of Myocardial Infarction and the current guidelines of the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand.[19] Using these different cutpoints has increased the diagnosis of acute coronary syndrome in females.[20]

Particularly in the early days of troponin testing, cardiologists were concerned over the large numbers of patients referred with small increases in troponin unrelated to acute coronary syndrome or acute myocardial infarction. In attempting to reduce these 'false positives', the 99th percentile was introduced as a diagnostic criterion, making troponin a 'rule-in' test.[21]

Cautions

In myocardial infarction there is an acute change in troponin concentration, however, patients may present days after their initial chest pain. Concentrations of cTnI may remain elevated for up to 4–5 days and cTnT up to 10 days, but two samples collected 2–3 hours apart may not be significantly different.

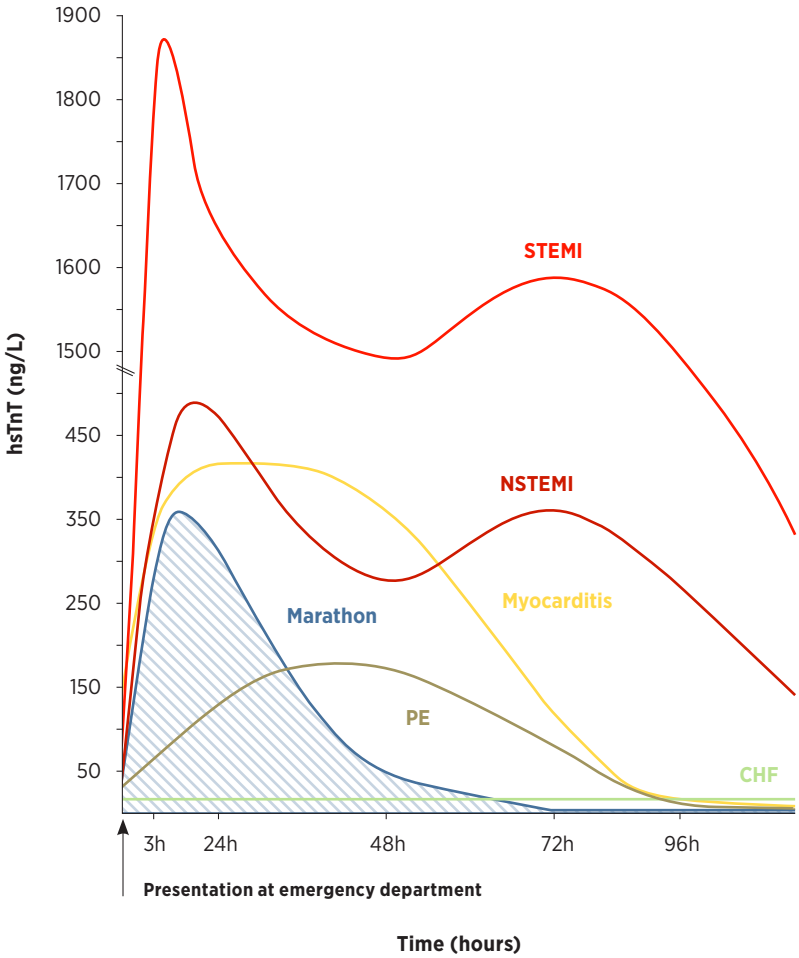
Troponin testing in general practice is not encouraged, as the troponin concentration alone does not rule out acute coronary syndrome.[19] A definitive risk stratification (with more than just a single measurement) is required. There are exceptions to this in rural or remote settings, or in patients presenting several days after symptom onset.

Cardiac troponins are measured by immunoassays which are prone to interference by endogenous immunoglobulins. They may bind to either of the troponins, or to the exogenous antibodies that are used in the assays. These interferences can be either positive or negative. If a troponin result does not fit with a strong clinical impression, talk to the laboratory about possible investigations for interference.[22]

Other causes of cardiac troponin elevation

A raised troponin concentration may be a sign of myocardial injury rather than infarction. Figure 2 shows the relative time courses of the major cardiac causes of chest pain including acute myocardial infarction. The shared pathway for myocardial damage is either an absolute or relative insufficiency of oxygen availability to meet myocardial requirements (Box 1). Elevated cardiac troponins in pulmonary embolism and in heart failure identify high-risk patients, but do not significantly influence management. In all conditions investigated to date, an

Fig. 2 **Troponin concentration–time curves**[26]



Cardiac troponin T kinetics for ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) are typically biphasic compared to monophasic kinetics in myocarditis, pulmonary embolism (PE), and endurance sports. The concentration of high-sensitivity troponin T measured can vary markedly after a marathon run (shaded area) and can even supersede that of, for example, NSTEMI. In chronic heart failure (CHF) troponin concentrations are persistent and often not elevated in the absence of an ischaemic episode.

hsTnt high-sensitivity cardiac troponin T concentration

elevated cardiac troponin is associated with a poorer prognosis in adults[23] and children.[24]

Although some drugs used in chemotherapy are cardiotoxic,[25] routine monitoring with troponins has not been adopted to identify patients at risk. In contrast, monitoring for the early transient cardiotoxicity which can occur when starting clozapine is more common.[4]

The finding of an unexpected elevated cardiac troponin requires explanation and clinical evaluation. For conditions in which the underlying cause is a mismatch of oxygen supply and demand, the expectation is a rise then fall in cardiac troponin (Fig. 2).[26] Compare this with drug-related causes where the changes may occur over a different timeframe and depend on the mechanism of damage and clearance of the drug. In chronic conditions such as end-stage renal failure, the troponin concentrations remain elevated, but are reversed following renal transplantation.

Conclusion

The measurement of cardiac troponins has a role in the diagnosis of acute coronary syndrome. However, many other conditions cause a rise in troponin concentrations. The importance of troponin in the diagnosis of acute coronary syndrome should, to some extent, be de-emphasised, with more weight given to the clinical presentation of the individual patient. It is a synthesis of clinical examination, ECG assessment, cardiac troponin measurement and imaging that may be needed to make the diagnosis of acute coronary syndrome.[27]

Health professionals need to be aware of the factors that can affect the results of troponin assays. A raised troponin concentration may be a sign of myocardial injury rather than infarction. ≺

Conflicts of interest: none declared

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NEW DRUGS

New drugs

Casirivimab and imdevimab

Aust Prescr 2022;45:58–9
https://doi.org/10.18773/austprescr.2022.013
First published 28 February 2022

Approved indication: COVID-19

Ronapreve (Roche)
casirivimab 120 mg/mL and imdevimab 120 mg/mL co-packaged in single-dose or multidose vials

Despite the provisional approval of remdesivir and sotrovimab for COVID-19 in Australia, there remains an urgent need for effective treatment and prophylaxis. Regimens combining casirivimab and imdevimab have now been provisionally approved for use in adults and adolescents 12 years and older, weighing at least 40 kg. These drugs are indicated for infected patients who have an elevated risk of progressing to severe COVID-19, but who do not need supplemental oxygen. Casirivimab and imdevimab have also been approved for post-exposure prophylaxis in individuals who are unvaccinated or have a medical condition that makes them unlikely to be protected by vaccination. The combination is not intended to be used as a substitute for vaccination against COVID-19.

Casirivimab and imdevimab are human monoclonal antibodies that target distinct epitopes of the spike protein of SARS-CoV-2. They block the virus from binding to the receptors on human cells. The aim of using two antibodies is to reduce the risk of viral resistance.

The drugs can be given together as an intravenous infusion or as separate subcutaneous injections. Doses for treatment and single-dose prophylaxis are casirivimab 600 mg and imdevimab 600 mg. If there is an ongoing need for prophylaxis, lower subsequent doses are given once every four weeks. For infection, the intravenous route is strongly recommended. Treatment should begin as soon as possible after a positive test for SARS-CoV-2 and not later than seven days after the onset of initial symptoms. Prophylaxis should be given as soon as possible after exposure to SARS-CoV-2.

The median times to reach the maximum serum concentrations following subcutaneous injection are 6.6 days for casirivimab and 6.5 days for imdevimab. Casirivimab and imdevimab are expected to be eliminated like other immunoglobulins. The half-lives are 30 days for casirivimab and 26 days for imdevimab. The effects of severe renal impairment or moderate-to-severe hepatic impairment are currently unclear. The antibodies are not renally excreted or metabolised by cytochrome P450 enzymes so pharmacokinetic interactions with concomitant drugs are unlikely. There have been no formal drug–drug interaction studies. As casirivimab and imdevimab bind to the spike protein that forms the basis of all COVID-19 vaccines, they may interfere with the development of effective immune responses to COVID-19 vaccines. These vaccines should therefore not be administered for at least 90 days after the antibodies.

There is an ongoing, placebo-controlled, clinical trial involving outpatients with confirmed COVID-19. An initial analysis of data from 275 symptomatic patients showed that intravenous casirivimab and imdevimab reduced the SARS-CoV-2 viral load. The largest effect was in patients with a high viral load, with most of the reduction occurring in the 48 hours following infusion. Patients who received the combination also reported fewer medical visits within the first 29 days (3% vs 6%).[1] Subsequent data from this trial showed a reduction in the viral load. COVID-19-related hospitalisation or death from any cause occurred in seven of 736 patients (1%) who received 1200 mg of the combination versus 24 of 748 patients who received a placebo (3.2%).[2]

A phase III trial studied subcutaneous casirivimab and imdevimab to prevent post-exposure infection in uninfected close contacts with household exposure to infected individuals. Overall, during a 28-day observation period, subcutaneous prophylaxis prevented symptomatic COVID-19 compared to placebo. Eleven of 753 patients (1.5%) who received the antibodies and 59 of 752 patients (7.8%) who received a placebo developed symptomatic COVID-19. Among these symptomatic patients, the median time to symptom resolution was shorter and the duration of a high viral load (more than 10^4 copies/mL) was shorter in the patients who received prophylaxis.[3]

Another part of this phase III trial investigated subcutaneous casirivimab and imdevimab for preventing progression in people with asymptomatic COVID-19 and household exposure to infected individuals. The combination reduced the progression to symptomatic infection. Symptoms developed in 29 of 100 participants (29%) who received the combination, compared with 44 of 104 participants (42.3%) given a placebo. The combination also reduced the duration of high viral loads, corresponding to a reduction in symptom duration of 5.6 days compared to placebo.[4]

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

Most of the adverse events encountered in the trials of intravenous and subcutaneous treatment were related to COVID-19. Injecting or infusing antibodies can cause hypersensitivity reactions. These reactions may include nausea, chills, dizziness or syncope, rash, urticaria and flushing. Anaphylaxis is rare.

The safety and efficacy of casirivimab and imdevimab in children and pregnant women are unknown.

Provisional approval of these drugs in Australia has been granted based on short-term efficacy and safety data. Continued approval for COVID-19 will depend on the evidence of longer term efficacy and safety. There will be a need to monitor for the emergence of viral variants that are resistant to the combination of casirivimab and imdevimab. The combination is unlikely to be effective against the Omicron variant.[5]

T T manufacturer provided additional useful information

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

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

NEW DRUGS

Aust Prescr 2022;45:60
https://doi.org/10.18773/austprescr.2022.014
First published 28 February 2022

Molnupiravir

Approved indication: COVID-19

Lagevrio (Merck Sharp & Dohme)
200 mg capsules

With the continuing healthcare burden of COVID-19, molnupiravir is another antiviral drug to be approved for use in Australia. Molnupiravir is a prodrug of N-hydroxycytidine, a ribonucleoside analogue that is incorporated into viral RNA, resulting in the inhibition of SARS-CoV-2 replication. The provisional approval is for the treatment of COVID-19 in adults who do not require oxygen and who are at risk of progressing to severe COVID-19.

Molnupiravir should be started as soon as possible after a diagnosis of COVID-19 and within five days of symptom onset. Four 200 mg capsules are taken every 12 hours, with or without food, for five days. The peak plasma concentration of N-hydroxycytidine is reached 1.5 hours after an oral dose of molnupiravir. N-hydroxycytidine has a half-life of about 3.3 hours and is metabolised via the same pathways as those involved in endogenous pyrimidine metabolism. Molnupiravir and N-hydroxycytidine do not induce or inhibit the major drug-metabolising enzymes or transporters, so drug interactions are unlikely. Doses do not need to be adjusted in patients with renal or hepatic impairment, although there are limited clinical trial data for patients with severe renal impairment or any degree of hepatic impairment.

A phase III trial randomised 1433 non-hospitalised, unvaccinated adults with confirmed mild-to-moderate COVID-19 who had developed symptoms no more than five days previously and who had at least one risk factor for progressing to severe COVID-19. At the time the trial was published, the Delta variant was the most common, being isolated in 58% of the participants with sequence data available. The primary efficacy end point was the incidence of hospitalisation or death from any cause at day 29. Of 709 participants who received 800 mg molnupiravir twice daily for 5 days, 48 (6.8%) were hospitalised or died, compared with 68 of 699 (9.7%) in the placebo group. One patient taking molnupiravir died, compared to nine in the placebo group. Although the confidence intervals overlapped, the efficacy outcomes were generally consistent across pre-specified subgroups including sex, time from symptom onset (0–3 vs more than 3 days), baseline COVID-19 severity (mild vs moderate) and risk factors for severe illness (age >60 years, obesity, cardiovascular disease).[1]

The most common adverse effects of molnupiravir include diarrhoea, nausea and dizziness, but these are typically mild or moderate. In the phase III trial, adverse events were reported in 216 of 710 participants (30.4%) in the molnupiravir group compared with 231 of 701 (33%) in the placebo group. Serious adverse events, such as pneumonia, were mostly related to COVID-19 rather than the drug or placebo.[1]

The safety and efficacy of molnupiravir administration for more than five days are unknown. Women are advised to use contraception during and for four days after treatment. Molnupiravir was found to be harmful in studies of pregnant animals so it is not recommended for pregnant or breastfeeding women. The medicine is not recommended in patients younger than 18 years of age due to a lack of safety and efficacy data.

Molnupiravir reduces the risk of hospitalisation or death in unvaccinated adults with COVID-19 who have a risk of progressing to severe COVID-19 when started within five days after symptom onset. However, the difference in the primary outcome from placebo is moderate, and approximately 15 patients must be treated for one to benefit.[2] In some subgroups, such as patients with diabetes, there was no benefit.[1] The potential benefit of molnupiravir for the treatment of vaccine breakthrough infections is currently unknown.

T manufacturer responded to request for availability

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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 European Medicines Agency and the Therapeutic Goods Administration.

Nirmatrelvir and ritonavir

Aust Prescr 2022;45:61
https://doi.org/10.18773/austprescr.2022.015
First published 28 February 2022

Approved indication: COVID-19

Paxlovid (Pfizer)
nirmatrelvir 150 mg film-coated tablets, ritonavir 100 mg film-coated tablets

Viral proteases are feasible targets for antiviral drugs. The main protease of SARS-CoV-2 plays a pivotal role in viral replication so inhibiting it could be an effective treatment for COVID-19. The antiviral drug nirmatrelvir, given with ritonavir, has been provisionally approved for the treatment of COVID-19 in adults who have an elevated risk of progressing to hospitalisation or death but do not require supplemental oxygen. This approval is based on incomplete data and may be revised with the publication of peer-reviewed results. The efficacy of the combination against the Omicron variant is not yet established. The combination is not approved for patients requiring hospitalisation for severe or critical COVID-19.

Nirmatrelvir works by binding to the SARS-CoV-2 3CL protease to prevent viral replication. To boost plasma concentrations, it is taken with ritonavir, an inhibitor of cytochrome P450 (CYP) 3A4 that blocks the metabolism of nirmatrelvir. Ritonavir itself is inactive against SARS-CoV-2.

The recommended regimen is two nirmatrelvir 150 mg tablets and one ritonavir 100 mg tablet taken together every 12 hours for five days, starting as soon as possible after a diagnosis of COVID-19 and within five days of the onset of symptoms. The tablets should be swallowed whole, with or without food, and not chewed, broken or crushed. As its metabolism by CYP3A4 is blocked by ritonavir, nirmatrelvir is mainly excreted unchanged in the urine and faeces. The mean half-life of nirmatrelvir with ritonavir is about seven hours. In patients with moderate renal impairment, a reduced dose of nirmatrelvir is recommended, but this adjusted regimen has not been clinically tested. The combination is contraindicated in patients with severe renal or hepatic impairment.

Nirmatrelvir and ritonavir are also contraindicated in patients who are taking drugs that are highly metabolised by CYP3A and drugs that are strong CYP3A inducers. There are many potential drug interactions.

A phase II/III double-blind, randomised controlled trial investigated the efficacy of the combination in unvaccinated patients at high risk of hospitalisation or death. This trial enrolled 2246 adults with COVID-19, mainly (98%) the Delta variant. Among those who were treated within three days of symptom onset, 0.7% (5/697) of the patients in the treatment group and 6.5% (44/682) of the placebo group were hospitalised within 28 days following randomisation. There were no deaths in the treatment group whereas nine patients in the placebo group died. When treated within five days of symptom onset, 0.8% (8/1039) of the treatment group and 6.3% (66/1046) of the placebo group were hospitalised within 28 days following randomisation. There were no deaths in the treatment group whereas 12 patients in the placebo group died.[1]

In this trial, up to 34 days after the last dose, 22.6% (251/1109) of the patients in the treatment group and 23.9% (266/1115) of the patients in the placebo group experienced treatment-emergent adverse reactions, which were usually mild in intensity. The most common adverse reactions were dysgeusia, diarrhoea, headache and vomiting. Nine (0.8%) patients in the treatment group and seven (0.6%) patients in the placebo group discontinued treatment due to an adverse event considered to be related to the drug or placebo.[1]

The safety and efficacy of nirmatrelvir and ritonavir in children and pregnant women are unknown. Breastfeeding should be discontinued during and for seven days after treatment. Ritonavir is likely to reduce the efficacy of combined hormonal contraceptives, so women are advised to use additional or alternative contraceptives during treatment and during a menstrual cycle after treatment.

Nirmatrelvir boosted with ritonavir should be used with caution for COVID-19 because of the potential for drug–drug interactions. The safety and efficacy of this treatment in vaccinated people have yet to be established.

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NEW DRUGS

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SARS-CoV-2 rS (NVX-CoV-2373) vaccine

Approved indication: prevention of COVID-19

Nuvaxovid (Biocelect)
multidose vials containing 5 microgram SARS-CoV-2 spike protein in adjuvanted suspension

SARS-CoV-2 rS, commonly referred to as Novavax, is the fifth vaccine to be provisionally approved in Australia for the prevention of COVID-19 in people 18 years of age and over. Its mechanism of action differs from that of the other vaccines. This vaccine is based on a genetically engineered form of the SARS-CoV-2 spike protein. It also contains an adjuvant to enhance the immune response of B and T cells.

The vaccine is supplied in multidose vials that should be stored at 2–8 °C. Each vial contains ten doses of 0.5 mL. The vaccine is given by intramuscular injection, with a second dose three weeks later.

A phase II trial took place in South Africa around the time the Beta variant of the virus emerged. This placebo-controlled trial randomised 4406 healthy adults, but, as approximately 30% of them already had antibodies against SARS-CoV-2, efficacy was assessed in 2684 seronegative participants who received two doses of the vaccine. Symptomatic COVID-19 developed in 1.1% (15/1357) of the vaccine group and 2.2% (29/1327) of the placebo group.[1]

A phase III trial in the United Kingdom randomised 15,187 adults to receive the vaccine or a placebo. Efficacy was assessed in 14,039 participants who were seronegative and received two doses. Symptomatic infection occurred, at least seven days after the second dose, in 0.14% (10/7020) of the vaccine group and 1.4% (96/7019) of the placebo group. Vaccine efficacy was calculated to be 89.7%. None of the fully vaccinated participants required hospital admission.[2]

Within the UK trial, a group of 431 participants was injected with influenza vaccine at the same time as their first dose of SARS-CoV-2 rS or placebo. Although there was no difference in the immune response to the influenza vaccine, there was a reduced response to the SARS-CoV-2 rS vaccine. Symptomatic COVID-19 developed in 1% (2/191) of the vaccine group and 4% (8/195) of the placebo group. Vaccine efficacy against COVID-19 was calculated to be 74.8% overall and 87.5% in participants under 65 years of age.[3]

A phase III trial in North America randomised 29,949 adults. Two doses of vaccine were given to 17,312 seronegative participants and 8140 received injections of placebo. After a median follow-up of three months, there were 14 cases (0.1%) of COVID-19 in the vaccinated group and 63 cases (0.8%) in the placebo group. Vaccine efficacy was calculated to be 90.4%. All cases of COVID-19 in the vaccinated group were mild.[4]

In the phase III trials, adverse reactions were more frequent following vaccination than in the placebo groups. Reactions were more common after the second dose, in younger people and in participants who received simultaneous influenza vaccine.[2-4] The most frequent reactions were injection-site tenderness (75%) or pain (62%). Systemic adverse effects reported in the trials included headache, arthralgia, myalgia and fatigue. The adverse reactions lasted for an average of one or two days.[2,4] Uncommon adverse events include hypertension and myocarditis. As anaphylaxis is a potential adverse reaction, patients should be observed for at least 15 minutes after being vaccinated.

When SARS-CoV-2 rS was evaluated, the median duration of follow-up after the second dose was 70 days. The phase III trials began before the current viral variants of concern emerged. Information about the efficacy and safety of this vaccine will therefore continue to evolve. At present, it is not approved for use in children or for booster doses. In theory this vaccine could be given in pregnancy but there are currently more data about using other COVID-19 vaccines during pregnancy and lactation.

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Fostemsavir

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Approved indication: HIV-1 infection

Rukobia (ViiV Healthcare)
600 mg film-coated tablets

Despite the wide availability of antiretroviral drugs for patients with HIV infection, treatment failure continues to occur because of problems such as antiretroviral drug resistance and drug intolerance. There is therefore a need for drugs that evade resistance and are well tolerated when multiple standard treatment regimens have been unsuccessful. Fostemsavir is the first of a new class of antiretroviral drugs called attachment inhibitors. It is approved for use, in combination with other anti-HIV drugs, for heavily treatment-experienced patients when viral suppression has not been possible with other regimens.

Fostemsavir is a prodrug of temsavir. The active drug works by binding to the HIV-1 virus, thereby inhibiting its interaction with CD4 receptors on T cells. This prevents the virus from entering and infecting T cells.

Fostemsavir is available as extended-release tablets. One tablet is taken orally twice daily with or without food. It is metabolised in the small intestine to temsavir, which has its peak plasma concentration two hours after oral administration with an absolute bioavailability of 26.9%. As temsavir is partly metabolised by cytochrome P450 (CYP) 3A4, fostemsavir should not be taken concomitantly with strong CYP3A inducers, including carbamazepine, phenytoin, rifampicin and St John's wort. Doses do not need to be adjusted in patients with renal or hepatic impairment. Temsavir has a terminal half-life of about 11 hours.

In a phase III multicentre trial of fostemsavir in patients with multidrug-resistant HIV-1 infection, the mean concentration of HIV-1 RNA decreased, from a median of 4.7 $\log_{10}$ copies/mL, by 0.79 $\log_{10}$ copies/mL after eight days of fostemsavir treatment in 203 patients, compared with a decrease of 0.17 $\log_{10}$ copies/mL after eight days of a placebo in 69 patients. Beyond eight days, the patients received an optimised background therapy plus open-label fostemsavir. After 48 weeks, 115 of 203 patients (57%) in the fostemsavir group and 31 of 69 patients (45%) in the placebo group showed a sustained virological response. Compared to the baseline median of 99 cells/mm^3, the mean CD4$^+$ T-cell counts increased by 139 cells/mm^3 in the fostemsavir group and 64 cells/mm^3 in the placebo group at 48 weeks.[1] The virologic response was further sustained with an increase in the CD4$^+$ T-cell count through 96 weeks.[2] A subgroup analysis of these results based on overall susceptibility scores revealed a lower virologic response in patients with high antiretroviral resistance compared to patients with partial resistance (34% at 24 weeks and 31% at 96 weeks vs 65% at 24 weeks and 88% at 96 weeks).[3]

Although most adverse events in the phase III trial were related to complications of advanced HIV infection, 92% of the participants reported experiencing at least one adverse effect, which was typically mild or moderate in severity.[1,2] In the analysis at 96 weeks, 7% of the patients had withdrawn because of adverse events, but only 3% were considered to be drug-related effects.[2] The most common adverse effects of fostemsavir include diarrhoea, headache, nausea, rashes and vomiting. Immune reconstitution inflammatory syndrome can occur in the first six months of administration in more than one in 100 individuals, which is a state of dysregulated hyperinflammation that occurs rapidly after the recovery of immune function. Liver chemistry monitoring is recommended in patients with hepatitis B or C co-infection. Fostemsavir should be used with caution in patients taking drugs with a known risk of torsade de pointes, with a history of QT interval prolongation or with cardiac disease.

There are limited data available on the use of fostemsavir in patients 65 years of age and older, and the safety and efficacy of fostemsavir are unknown in pregnant women. The medicine is not recommended in patients younger than 18 years of age due to a lack of safety and efficacy data.

Fostemsavir taken with other HIV medicines suppresses the viral load with a sustained long-term response in patients with multidrug-resistant HIV-1 infection who have few remaining options for active therapy due to resistance, intolerance or safety considerations. Fostemsavir does not cure HIV-1 infection or acquired immunodeficiency syndrome, but it can minimise deterioration of the immune system in heavily treatment-experienced patients.

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Lanadelumab

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Approved indication: hereditary angioedema

Takhzyro (Takeda)
pre-filled syringes containing 150 mg/mL solution for injection

Hereditary angioedema is a rare autosomal dominant disorder caused by the deficiency or dysfunction of C1 esterase inhibitor. This results in increased plasma kallikrein activity and excess production of the vasodilator bradykinin, which leads to unpredictable recurrences of severe swelling in subcutaneous or submucosal tissues that are potentially fatal. One approach to preventing angioedema is therefore to control the activity of kallikrein.[1] Lanadelumab is a fully human monoclonal antibody that inhibits active plasma kallikrein proteolytic activity and thereby reduces bradykinin production.

Lanadelumab is given by subcutaneous injection every two weeks. The half-life is 14–15 days, so it takes about 70 days to reach a steady state. No dose adjustment is recommended in mild-to-moderate renal impairment, but the effects of severe impairment and hepatic impairment are unknown.

The phase III, multicentre Hereditary Angioedema Long-term Prophylaxis (HELP) trial randomised 125 patients to receive lanadelumab 150 mg (n = 28) or 300 mg (n = 29) every four weeks, 300 mg every two weeks (n = 27), or a placebo (n = 41). During a four-week run-in period, these patients had a mean of 3.2–4 attacks of angioedema. After 26 weeks, lanadelumab reduced the attack rate to 0.26–0.53 attacks/month compared with 1.97 attacks/month in the placebo group. Among the patients receiving injections of lanadelumab every two weeks, 44.4% remained attack free.[2] The benefits were seen from the first dose and were sustained throughout the trial.[3] Improvements in health-related quality of life following lanadelumab treatment were also noted.[4]

The most common adverse events during the HELP trial were injection-site reactions, which affected 52.4% of the patients receiving lanadelumab compared with 34.1% of the placebo group. Headache and dizziness were also more frequent than in the placebo group. Antidrug antibodies, but few neutralising antibodies, were detected in some patients. No deaths or severe treatment-emergent adverse events were reported.[2]

Based on the trial results, the recommended starting dose of lanadelumab is 300 mg. This may be reduced to 300 mg every four weeks if the attacks are well controlled. As children were not included in the HELP trial, lanadelumab is indicated for the prevention of recurrent episodes of hereditary angioedema in patients 12 years of age and older.

The safety and efficacy of lanadelumab are unknown in pregnant or lactating women, and information is limited in patients older than 65 years of age.

Regarding longer term efficacy and safety, an open-label extension of the HELP trial found that 300 mg lanadelumab given every two weeks reduced the mean attack rate from 3.1 attacks/month in the four weeks leading up to the trial to 0.4 attacks/month in the first four weeks of the trial. After a mean of 29.6 months, 75.5% of 204 patients achieved a reduction in the attack rate of at least 90%, and 37.3% remained attack free. The injection-site reactions were similar to those in the initial HELP trial, with no deaths or severe treatment-emergent adverse events.[5]

Lanadelumab is well tolerated and prolongs the attack-free period in patients with hereditary angioedema. With a sustained decline in attacks, the frequency of doses may be reduced. Clinicians should, however, continue to monitor for breakthrough attacks.

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NEW DRUGS

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Ravulizumab

Approved indication: paroxysmal nocturnal haemoglobinuria

Ultomiris (Alexion)
vials containing 10 mg/mL, 100 mg/mL concentrated solution

Paroxysmal nocturnal haemoglobinuria is a rare cause of haemolytic anaemia. Affected patients have a mutation that results in a loss of function of a critical enzyme involved in linking proteins to the plasma membrane of haematopoietic cells. These proteins include the complement inhibitory proteins, so patients are vulnerable to complement-mediated intravascular haemolysis. They are also at risk of thrombosis and bone marrow failure. Management was generally limited to supportive care, such as transfusions of red blood cells, unless a bone marrow transplant was possible. Treatment changed with the approval of eculizumab. This is a monoclonal antibody that binds to complement protein C5 to stop the complement cascade. Although eculizumab has improved outcomes for patients, it has to be infused every two weeks. This is one of the reasons for the development of ravulizumab.

Ravulizumab is a genetically engineered monoclonal antibody. It binds with high affinity to complement protein C5. Ravulizumab is diluted then slowly infused according to protocol. A loading dose enables immediate achievement of a steady state and inhibition of C5. As ravulizumab has a half-life of about 50 days, maintenance doses only need to be infused every eight weeks. Ravulizumab is expected to be metabolised like other immunoglobulins, so no dose adjustments have been recommended for patients with liver or kidney disease.

Ravulizumab has been evaluated in patients with paroxysmal nocturnal haemoglobinuria who had not previously received a complement inhibitor and in those who were being treated with eculizumab. These two open-label trials assessed haemolysis by measuring concentrations of lactate dehydrogenase.[1,2]

The trial of previously untreated patients randomised 125 to receive ravulizumab and 121 to receive eculizumab for 26 weeks. Treatment resulted in lactate dehydrogenase concentrations returning to normal in 53.6% of the ravulizumab group and 49.4% of the eculizumab group. Breakthrough haemolysis affected 4% and 10.7%. No transfusions were needed in 73.6% of the ravulizumab group and 66.1% of the eculizumab group.[1]

In the trial of patients receiving eculizumab, 98 were randomised to continue while 97 were switched to infusions of ravulizumab. After 26 weeks, 66% of the ravulizumab group had normal concentrations of lactate dehydrogenase compared with 59.2% of the eculizumab group. The mean change in concentration was a decrease of 0.82% with ravulizumab and an increase of 8.39% with eculizumab. None of the patients taking ravulizumab had breakthrough haemolysis compared to five of the eculizumab group. Fewer patients (12 vs 17) in the ravulizumab group required transfusions.[2]

Headache was a frequent adverse effect reported in the trials. It affected 32% of the patients given ravulizumab and 26% of those given eculizumab. Other adverse events occurred at similar rates in both groups. The effect on the complement system increases the susceptibility of patients to meningococcal infection. Meningococcal vaccine before treatment with ravulizumab is therefore recommended.

Statistical analysis shows that ravulizumab is non-inferior to eculizumab.[1,2] Although the duration of each infusion is longer, patients are likely to prefer the reduced frequency of ravulizumab infusions. The current approval is limited to adults, but ravulizumab is being studied in children.

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EDITORIAL

Oral antivirals for mild–moderate COVID-19: a panacea or a logistical and clinical conundrum?

In Australia COVID-19 is currently characterised by the Omicron variant in a population with high rates of primary vaccination, but moderate rates of booster doses. Healthcare professionals and health systems are facing new challenges with the increasing spread of SARS-CoV-2 through the community, the potential emergence of new mutations and the relaxation of public health restrictions. Although vaccination has significantly reduced morbidity and mortality from COVID-19, high case numbers mean that interventions to reduce hospital admissions and prevent long-term complications remain highly desirable.[1] These interventions are particularly important in people who are not fully vaccinated, and those who are immunosuppressed and may not develop adequate antibody responses from immunisation.

The Omicron surge heightened the perceived need for drugs to prevent or treat severe disease in patients infected with SARS-CoV-2. Approval of new drugs was expedited by regulatory agencies, such as the Therapeutic Goods Administration (TGA) via the provisional approval pathway.

Multiple therapeutic options for COVID-19 are now available. These include parenteral anti-spike protein monoclonal antibodies (sotrovimab, casirivimab/imdevimab), oral antivirals (nirmatrelvir/ritonavir, molnupiravir) and parenteral antivirals (remdesivir). However, clinical trial data are limited and were usually collected before the Omicron variant emerged. The considerations about the use of these treatments are complex. Each drug has nuances related to the patient population they were studied in, the strength of their apparent effects and the practicalities of how these treatments could be used in different populations. This leads to uncertainty about how to facilitate access to effective therapies and how to use them safely.

Among the new oral drugs, nirmatrelvir/ritonavir is a potentially effective antiviral combination. It reduced the absolute risk of hospitalisation due to COVID-19 by 5.8% within 28 days of randomisation.[2] However, this combination is not without risk, with a high certainty for harm if potentially significant drug interactions with ritonavir are not mitigated.[3] Molnupiravir had a marginal benefit of 2.9% in reduced hospitalisation.[4] The pharmacoeconomic benefits, in terms of hospital bed days saved for both treatments, remain to be shown.

Some of these new drug approvals appear to be based on preliminary clinical data from single placebo-controlled, drug company-sponsored clinical trials. The information that was available to clinicians and clinical practice guideline panels at the time of approval was sometimes in the form of pre-print articles, press releases or summary data from regulatory agencies, rather than peer-reviewed publications. However, the evidence of clinical effectiveness was mainly from a patient cohort that now forms only a small part of the community – unvaccinated people infected with the Delta variant. These rapid approvals create a situation where postmarketing surveillance is crucial to ensure any benefits are derived without harm. The feedback of data about outcomes will be essential to inform future clinical use and continuing TGA approval.[5]

The currently available evidence presents a challenge to the use of the new drugs. Their clinical effect was seen in unvaccinated patients, with infections confirmed by polymerase chain reaction, who had a high risk of developing severe disease. The trials took place before the emergence of the Omicron variant, which is thought to have a lower virulence than previous variants. Most Australians are vaccinated and confirmation of infection is now by self-administered rapid antigen testing, which may result in false positives. There are also no head-to-head studies comparing nirmatrelvir/ritonavir with molnupiravir to guide treatment recommendations and delineate which patient groups should have priority access to the new oral drugs. It is impractical to restrict the use of these drugs to patients with particular comorbidity profiles. Eligibility criteria may not be completely reflective of the inclusion criteria used in the trials. An additional challenge is the change to the definition of who is considered to be 'fully vaccinated'. The drugs are now being used in patients who have received two doses of vaccine but have not received a booster dose. It is unknown whether the drugs will remain clinically effective or cost-effective in these people.

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EDITORIAL

Oral antivirals for mild–moderate COVID-19: a panacea or a logistical and clinical conundrum?

Access to the intravenous agents is limited by the location and capacity of infusion centres. This will encourage the use of oral antivirals in the community, despite many prescribers having little experience with these drugs and the absence of long-term safety data, including information about antiviral resistance. Current treatments for COVID-19 are predominantly used under supervision in highly resourced hospital settings with daily monitoring of patients. However, in order to enable wider and more rapid access in regional, rural and remote areas of Australia, the prescribing and dispensing of the new oral drugs will move from specialised COVID-19 units attached to hospitals to primary care, supported by the Pharmaceutical Benefits Scheme (PBS). Molnupiravir has been listed on the PBS[6] with uncertain ease of access in the community. The PBS criteria ideally should complement the national evidence-based COVID-19 Living Guidelines to prevent inequity of access and the use of drugs in patients who are unlikely to benefit. However, the rapid distribution of oral drugs directly to residential aged care and health services for Aboriginal and Torres Strait Islander people, while intended to enable immediate access for vulnerable patient groups, may also have increased risks through a lack of guidance and education to support appropriate prescribing. These risks need to be mitigated. Healthcare systems must therefore determine how to maximise the benefits and safety of the new drugs and create a sustainable multidisciplinary, collaborative and responsive hospital-community model.

Rapid TGA approval and PBS listing of oral drugs will lead to a significant shift in the way that COVID-19 patients have been managed up to this point. It potentially adds to the risk of medication misadventure when community prescribers have limited access to specialist advice and support. Comprehensive guidelines and decision support for GPs and community pharmacists are required to ensure the safe use of these oral antiviral drugs, particularly in relation to drug interactions.[7]

The COVID-19 Living Guidelines for using the new drugs will change when more evidence emerges. To further inform decisions around ongoing and future drug approvals, purchasing, distribution and access, it is essential to capture data to evaluate the real-world outcomes of these new therapies. ◀

Conflicts of interest: Andrew Henderson has participated in advisory board meetings for MSD. Jason A Roberts is on advisory boards for Pfizer, MSD and Gilead, and has received speaking fees from Gilead.

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