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CONTENTS

EDITORIAL

Fast-track pathways for drug approvals: the Australian experience so far

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In 2016, the Australian Government announced that the Therapeutic Goods Administration (TGA) would establish two new pathways for the rapid approval of therapeutic advances and life-saving drugs.[1] These are the priority review and provisional approval pathways. The aim is to make the medicines available to the people who need them sooner than the usual regulatory process.

A drug is only eligible for a fast-track pathway if its proposed primary indication is for the treatment, prevention or diagnosis of a life-threatening or seriously debilitating condition. The drug must also represent a major therapeutic advance in safety or efficacy relative to already approved treatments. In addition to new drugs, new indications are eligible for the fast-track pathways.

The priority review pathway aims to complete the evaluation of a full set of data in 150 working days rather than the 255 legislated working days for a standard approval. A priority review requires a complete dossier based on clinical trial data, just like the standard approval process. For this reason, if the priority review is successful, the drug receives full registration on the Australian Register of Therapeutic Goods.

From January 2018 to July 2019, the TGA approved applications for 64 new chemical entities and 98 extensions of indications. Up to July 2019, 15 applications had been approved by priority review, including four new chemical entities and 12 extensions of indications. Twelve of these approvals were for drugs used in cancers where existing therapies have very limited efficacy. The time taken for priority reviews ranged from 80 to 147 working days with an average of 113 working days.

Before a drug can be evaluated under priority review, its sponsor, usually a pharmaceutical company, must apply for a determination that the drug is eligible for this pathway. An example of how the TGA makes a determination is alectinib for lung cancer.

Alectinib was already registered on the Australian Register of Therapeutic Goods for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer. However, it was only approved for patients who had progressed on or were intolerant of crizotinib. The sponsor sought a new primary indication, that would extend the use of alectinib to first-line treatment, and for this to be considered for priority review.

The sponsor provided a clinical rationale for approving the new indication based on a phase III randomised trial. This compared alectinib to crizotinib in patients with untreated ALK-positive non-small cell lung cancer. The trial found that alectinib had a significant benefit on the primary efficacy outcome (progression-free survival), particularly in the central nervous system. Alectinib also had a better overall safety profile than crizotinib. The findings of the trial constituted substantial evidence that alectinib would be a major therapeutic advance compared to crizotinib.

The TGA determined that the submitted clinical data made the new indication eligible for priority review. After evaluation of the complete dossier, this indication for alectinib was approved for full registration on the Australian Register of Therapeutic Goods.[2]

The provisional approval pathway, in contrast to the priority review pathway, enables a time-limited registration of a promising drug, based on preliminary (usually phase II) clinical data.[3] If approved, the drug will be available for two years and the drug's sponsor can apply for extensions up to a total of six years. Typically, the final stages of clinical trials (phase III) that address the safety, quality and efficacy of a medicine can take several years. By accepting applications for assessment before these trials are completed, a medicine could be brought to market potentially years sooner than under previous processes.

Up to July 2019, 13 applications had been determined as eligible for the provisional approval pathway. The first approval using this pathway was for an extension of indications for pembrolizumab.

The TGA only grants provisional approval if the potential benefit of early availability outweighs the risks of incomplete data about the drug. For example, a drug may be potentially life-saving, but if trial data on morbidity or mortality are not available, or the results are based on surrogate end points that have not been shown to reliably predict clinical benefit, it may not be eligible for this pathway.

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As a condition of provisional approval, the sponsor must provide a Risk Management Plan (required for all new chemical entities and major extensions of indication) and submit comprehensive clinical safety and efficacy data within the provisional time period and in accordance with this plan. If the sponsor does not follow this plan, they will not meet their conditions of registration and the TGA may revoke or not extend the drug's provisional registration. Successful evaluation of these confirmatory data will result in a transition to full registration on the Australian Register of Therapeutic Goods. The initial provisional approval and continuing registration is only permitted if the TGA is satisfied that confirmatory data will be submitted within six years.

Postmarketing surveillance of all prescription drugs is ongoing and there have been recent updates to enhance our postmarket monitoring and compliance framework. As part of these changes, provisionally registered medicines will be given high priority for postmarketing surveillance activities. As of January 2018, new drugs and new indications are marked with a black triangle symbol ▼ on the Product Information and Consumer Medicines Information.[4] This is a reminder to report adverse events that may be associated with the drug as this reporting continues to be a valuable supplement to information from sponsors and other international regulators. It does not mean that there are known safety problems, only that the TGA encourages prescribers, sponsors, pharmacists and patients to report adverse events as the medicine is new, so it can build a full picture of the drug's safety profile. This is particularly the case for provisionally registered drugs.

The eligibility criteria for both of these fast-track pathways ensure that they are restricted to those drugs that patients need most urgently. Adverse event reports help the TGA to monitor the safety of these medicines, particularly when they are new to market. The pathways increase the options for patients with life-threatening or debilitating conditions, while maintaining Australia's strong national standards for safety, quality and efficacy. ≺

The authors are either current or former employees of the Therapeutic Goods Administration.

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LETTERS

Letters to the Editor

Shorter antibiotic courses, but why?

Aust Prescr 2019;42:120
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Thanks for the article on antimicrobial duration for common infections.[1] I both hated it and welcomed it. I hated it because it contradicted prior teaching which I have long preached, and welcomed it for the benefits cited and because it is evidence based.

It would be useful for prescribers to know why shorter antibiotic courses are as effective as standard ones so they may comply and educate the patient. Is it the case that the antibiotic 'stuns' the organism allowing the immune system to acquire an enhanced ability to fight it which is adequate once the antibiotic is ceased? I realise this sounds like a lovely theory, but is there any evidence for this notion or any other proven reason?

An alternative or additional explanation to tell the patient could be simply 'Don't be surprised by the short course I have prescribed. The latest evidence is that it is sufficient and has the added benefit for you of reducing adverse effects.'

Incorporation of artificial intelligence in prescribing software which linked the diagnosis with the prescribing of the appropriate reduced antibiotic quantities (by default), along with the reason and what to say to the patient, would be useful.

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Heather Wilson, one of the authors of the article, comments:

Antibiotics target a variety of molecules in bacteria that can kill the bacteria or halt their growth. Successful treatment of an infection relies on multiple factors, including a balance between the appropriate antibiotic treatment and the actions of the immune system. Sterility in any infection is not necessary except in a few key circumstances.

The key to the current recommendations on antibiotic duration is based on two main points. First, we now have empirical evidence that shorter courses are nearly always as effective as standard ones, whereas previous recommendations were largely arbitrary. Second, it was previously thought that you had to use enough antibiotic to prevent the development of resistance. We now understand that many of the adverse effects that are related to antibiotic use, for example antibiotic resistance, candidiasis and *Clostridium difficile* infection, are increased with prolonged antibiotic therapy.

In terms of resistance, it is often not the initial infecting organism that is the problem. Instead longer antibiotic exposures result in greater pressure to select for antibiotic resistance in other commensal bacteria that may then go on to cause infection in the future.

The idea of having syndrome-based prescribing information linked into prescribing software is a good one. It is something that I hope to see in the future, but as far as I know is not available now. In the meantime, guidance may be sought from local guidelines. The latest version of Therapeutic Guidelines: Antibiotic has new resources to support primary care practitioners in antimicrobial prescribing, including shared decision-making with patients.

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.

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Drug-induced bruxism

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We sincerely thank Stephen Duma and Victor Fung for their comprehensive article on drug-induced movement disorders.[1] While the review is thorough, the adverse effect of drug-induced bruxism has been omitted.

Bruxism is defined as 'a repetitive jaw-muscle activity characterised by clenching or grinding of the teeth, or bracing or thrusting of the mandible'.[2] Bruxism occurs in adults and children, with a systematic review reporting an incidence of 18.6% in adults. Orofacial consequences include jaw-muscle hypertrophy, tooth wear and crack development, fractures of tooth restorations and pain associated with the teeth and surrounding musculature.[3]

Bruxism is an under-recognised adverse drug reaction particularly associated with use of antipsychotics and selective serotonin reuptake inhibitors.[4-7] A recent systematic review of case reports found it was most commonly reported with fluoxetine, venlafaxine and sertraline.[7] The median time for symptom onset is 3–4 weeks although it may occur even after a few doses. The frequency appears to be dose-dependent and symptoms usually take 3–4 weeks to resolve with drug cessation.[7] Antipsychotics are also associated with bruxism due to their inhibitory effect on dopamine-2 receptors.[5,6]

While the movement disorder tardive dyskinesia was mentioned in the article and the orofacial manifestations were alluded to, it is important to highlight that orobuccolingual dyskinesias (i.e. involving the face, mandible, lips and tongue) are often the first manifestation and the most common form of tardive dyskinesia.[8] They usually present as lip-smacking, grimacing, rapid eye blinking and dyskinetic tongue movements such as protrusion and tongue rolling.[9] In addition, they can also appear after medium- to long-term treatment with antipsychotic medicines, with a latency of up to 1–2 years.[8]

Clinical and registered indications for antidepressants and antipsychotics have expanded over recent years to include conditions such as anxiety, mania, behavioural disturbances of dementia and autism. It is therefore likely that the incidence of these orofacial drug-induced movement disorders will increase as these medicines are prescribed more frequently across a wider patient age range.[10]

Orofacial manifestations of drug-induced movement disorders are significant adverse effects which can affect both quality of life and medication adherence.[11] Raising awareness of this often-overlooked adverse effect is therefore essential.

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Stephen Duma and Victor Fung, the authors of the article, comment:

Bruxism, as well as related symptoms of jaw pain and headache, are relatively common yet often under-recognised adverse drug reactions. They were not mentioned in our article because we focused on drug-induced movement disorders that are typically referred to movement disorders specialists. While temporomandibular joint-related symptoms including bruxism are also encountered and sometimes managed by movement disorders specialists, they are usually initially referred to other specialists, including dentists, orthodontists, ear, nose and throat specialists, oromaxillofacial and other oral health specialists.

Bruxism can be managed in various ways. Sleep bruxism is typically initially treated with a splint.[1] This can also be applied to awake bruxism, however compliance may be an issue. Psychosocial approaches can also be used. However, botulinum toxin injections into the masseter and temporalis muscles are being used more frequently as an effective treatment with minimal adverse effects.[2]

We acknowledge that orobuccolingual dyskinesia is often the commonest form of tardive dyskinesia and awareness and recognition of this disorder will enable referral for appropriate treatment.

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LETTERS

Flu vaccination when travelling between countries

Aust Prescr 2019;42:122
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I really enjoyed the article and podcast on the prevention and treatment of influenza.[1]

This year the flu was very common in Japan. As a lot of Australian tourists go to Japan for sightseeing and skiing, I wanted to ask:

- can travellers have a flu shot in Japan in January or February even if they have had the flu shot in Australia in the autumn of the previous year?
- is the flu shot in Australia still effective at preventing influenza in Japan?
- do you have any suggestions to prevent bringing the flu virus from Japan to Australia?

Nowadays we see patients with flu all year round. I think one of the causes of this is that people bring the flu virus from the northern hemisphere.

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Dominic Dwyer, one of the authors of the article, comments:

There is no doubt that influenza viruses circulate between the northern and southern hemispheres, and travellers contribute to this circulation. This complicates advice to travellers from Australia to Japan, especially during the Japanese winter.

Influenza-specific antibodies induced by the vaccine last for around six months. This means that vaccine administered in April–May before the Australian winter is unlikely to have any significant benefit for people going to the northern hemisphere winter in January–February. It would therefore be reasonable to offer vaccine to Australians travelling to the northern hemisphere in winter assuming the vaccine is available in Australia at this time.

It takes about two weeks for vaccine-induced antibodies to appear, so vaccination on arrival in Japan during winter is unlikely to help most travellers. Advice about personal protection and handwashing during the influenza season is helpful, as is early diagnosis and neuraminidase inhibitor treatment in individuals with an influenza-like illness.

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ARTICLE

Venous thromboembolism: current management

SUMMARY

Anticoagulation is indicated in most cases of venous thromboembolism.

Monotherapy with rivaroxaban or apixaban is the preferred option for most adults with acute venous thromboembolism.

There are no recommended dose reductions for rivaroxaban or apixaban in venous thromboembolism, unlike for atrial fibrillation.

The initial duration of anticoagulation is usually three months.

Extended treatment with low-dose rivaroxaban or apixaban is effective in preventing recurrence in patients with a continuing increased risk of thromboembolism. Both drugs have low rates of major bleeding.

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Keywords
anticoagulants, apixaban, rivaroxaban, venous thromboembolism, warfarin

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Introduction

Therapy for venous thromboembolism traditionally involved parenteral anticoagulation and subsequent warfarin. However, this approach has changed with the introduction of the direct oral anticoagulants:

- rivaroxaban and apixaban (factor Xa inhibitors)
- dabigatran (direct thrombin inhibitor).

Venous thromboembolism can present as deep vein thrombosis or pulmonary embolism. It has an incidence of about 1.5 in 1000 people per year and a lifetime prevalence of more than 5%.[1] The diagnosis requires urgent assessment. Anticoagulation is usually needed to reduce the risk of fatal pulmonary embolism and morbidity from recurrent venous thromboembolism, post-thrombotic syndrome and pulmonary hypertension.[2,3]

When compared with warfarin, direct oral anticoagulants are as effective in preventing recurrent venous thromboembolism, and have a strong trend to less bleeding. They also have the advantage of having few food and drug interactions and do not require laboratory monitoring.[4-7] Apixaban and rivaroxaban can be used as monotherapy and are now the preferred option for most adults with acute venous thromboembolism.

Before considering anticoagulation

All patients require a full blood count, biochemical analysis and coagulation studies. Pregnancy should be excluded in women of childbearing age.[8] Testing for thrombophilias, such as the factor V Leiden and prothrombin gene mutations, is generally unhelpful as the presence of these abnormalities has little influence on the risk of recurrent venous thromboembolism and therefore on determining the duration of anticoagulation. It is reasonable to test for the antiphospholipid antibody syndrome in patients with unprovoked venous thromboembolism who are under 45 years of age.

Drug interactions with direct oral anticoagulants are infrequent. However drugs that significantly alter the function of P-glycoprotein (including azole antifungals, rifampicin, amiodarone or quinidine) or cytochrome P450 3A4 (including HIV protease inhibitors, clarithromycin, carbamazepine and rifampicin)[9,10] may influence their anticoagulant effect. Seek a specialist opinion for patients taking any of these medicines.

Initial anticoagulation

Most patients can be started on monotherapy with rivaroxaban or apixaban without the use of parenteral anticoagulant therapy. After an initial period of more intense oral anticoagulation, therapy is reduced to maintenance dosing (see Table 1).

Table 1 **Dosing schedule for rivaroxaban and apixaban in venous thromboembolism**

Drug	Initial phase	Maintenance phase up to six months	Renal contraindication
Rivaroxaban	15 mg twice daily for 21 days	20 mg once daily	CrCl* <30 mL/min
Apixaban	10 mg twice daily for 7 days	5 mg twice daily	CrCl* <25 mL/min

* calculated creatinine clearance (CrCl) based on the Cockroft-Gault formula

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Correct dosing of both the initial period and maintenance treatment is extremely important to ensure efficacy. There is no dose reduction based on age, low weight or moderate renal impairment with rivaroxaban and apixaban, in contrast to their use in atrial fibrillation. However, they are contraindicated in severe renal impairment (creatinine clearance below 30 mL/min).

Dabigatran is approved for the treatment of venous thromboembolism, but is not currently subsidised through the Pharmaceutical Benefits Scheme for this indication. Unlike rivaroxaban and apixaban, a parenteral anticoagulant (e.g. enoxaparin) needs to be used for five days before starting dabigatran. As dabigatran is predominantly eliminated via the kidneys, it is contraindicated in severe renal impairment.[9]

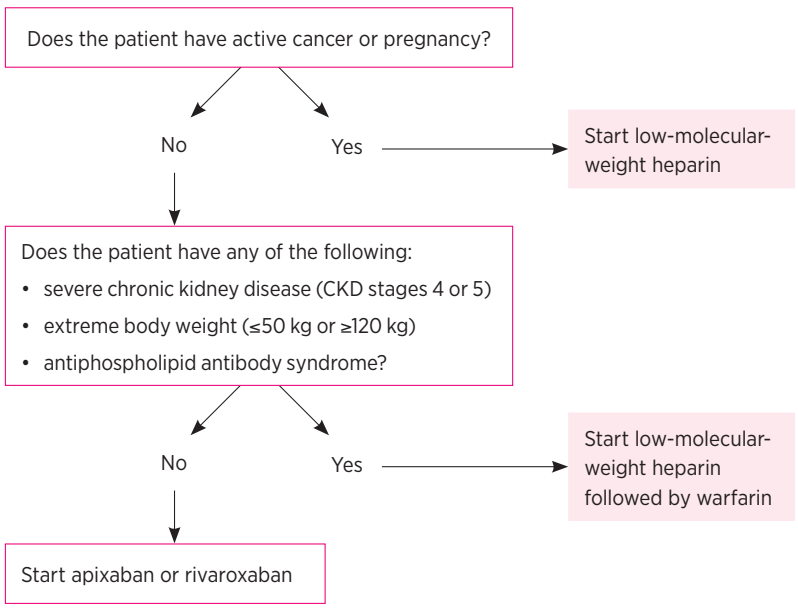
Which anticoagulant is best for my patient?

Rivaroxaban or apixaban are generally favoured over dabigatran or warfarin as they do not require a period of parenteral anticoagulation or routine laboratory monitoring (see Fig.). However, there are several circumstances in which a heparin overlapping with warfarin remains the standard of care. These include:

- severe chronic kidney disease (CKD stages 4 or 5)
- extremes of body weight (≤50 kg or ≥120 kg)
- antiphospholipid antibody syndrome.[11]

All oral anticoagulants are contraindicated in pregnancy. A low-molecular-weight heparin, such as enoxaparin or dalteparin, remains the standard of care.

Fig. **Initial treatment of venous thromboembolism**



Patients with venous thromboembolism associated with active malignancy should also be treated with a low-molecular-weight heparin as this is more effective than warfarin in preventing recurrent venous thromboembolism.[12] There is emerging evidence that a direct oral anticoagulant may be a reasonable alternative in some cancers.[13,14] However, this is not yet routine clinical practice and should only be considered in consultation with a specialist.

Duration of initial treatment

The duration of initial treatment is determined by the location of the thrombosis.

Proximal deep vein thrombosis and pulmonary embolism

Anticoagulation is indicated for patients with proximal deep vein thrombosis and pulmonary embolism as it reduces the development of pulmonary embolism and extension of deep vein thrombosis. It also reduces the mortality associated with pulmonary embolism.[3]

Anticoagulation is required for at least three months. A shorter duration (e.g. 4–6 weeks) is associated with higher rates of recurrence.[15,16]

Distal deep vein thrombosis

Distal deep vein thrombosis is confined to veins distal to the popliteal vein, including the tibial and peroneal veins and the calf muscle veins (soleal and gastrocnemius). It has a lower risk of extension and of associated pulmonary embolism than proximal deep vein thrombosis.[17,18]

Clinical trials of anticoagulation for distal deep vein thrombosis have discordant results. Some suggest six weeks to three months of anticoagulation is needed while others question the need for anticoagulation at all.[19-22] A common practice is to treat with therapeutic anticoagulation for six weeks to three months for symptomatic patients with a low bleeding risk and isolated distal deep vein thrombosis. This is reflected in new Australasian guidelines.[23] If the bleeding risk is considered high (e.g. active bleeding, thrombocytopenia with platelets <50 x 10^9/L), surveillance ultrasound (at least two ultrasounds over two weeks) is a reasonable alternative. If ultrasound shows an extension of the deep vein thrombosis, anticoagulation should be given.

Extended anticoagulation for unprovoked venous thromboembolism

Venous thromboembolism often recurs. Ongoing anticoagulation reduces recurrence by about 80%. However, it is required long term and is associated with bleeding and inconvenience. An assessment of the risks of recurrence and bleeding is required to determine if extended anticoagulation is indicated. The most important predictors of recurrence include proximal

deep vein thrombosis or pulmonary embolism, a history of previous venous thromboembolism and male sex[16,24] (Table 2). The most common thrombophilias – heterozygous factor V Leiden and prothrombin gene mutations – have little effect on recurrence and do not guide the duration of anticoagulation.[25]

Anticoagulation is stopped after three months if the risk of recurrence is low (e.g. surgically provoked venous thromboembolism, distal deep vein thrombosis). It is continued indefinitely if the risk is high (e.g. previous venous thromboembolism, active cancer, antiphospholipid antibody syndrome). However, in many cases there is an intermediate risk of recurrence. In these patients, ongoing low-intensity anticoagulation is safe and effective. Low doses of apixaban (2.5 mg twice daily) and rivaroxaban (10 mg daily) are as effective in preventing recurrence as full doses and have a favourable bleeding profile.[26,27] Major bleeding in these patients using low-dose anticoagulation is similar to those not receiving anticoagulants. Strong consideration should be given to indefinite low-intensity anticoagulation for patients at intermediate risk of recurrence (e.g. non-surgical or unprovoked venous thromboembolism, especially in males). Patient preference is extremely important in this decision making.[26,27]

In unprovoked venous thromboembolism, low-dose aspirin reduces rates of recurrence,[28] but to a much lower extent than low-dose rivaroxaban or apixaban. Aspirin is not recommended for extended treatment of venous thromboembolism, but it may be considered if the decision has been made to stop anticoagulation and a patient requires aspirin for another indication.

Predictors of bleeding include previous major bleeding during anticoagulation, thrombocytopenia and the presence of a lesion with a high bleeding risk (e.g. active peptic ulceration). These are uncommon and specialist advice should be sought if present.

Laboratory testing

Blood monitoring is not routinely required for direct oral anticoagulants due to their predictable pharmacokinetics. It is occasionally considered in circumstances such as preoperatively in patients with renal insufficiency, following an adverse event or to assess adherence. Testing includes the dilute thrombin time for dabigatran, or a chromogenic anti-Xa assay for rivaroxaban and apixaban.[29]

Direct oral anticoagulants may interfere with routine and special coagulation testing. Of note, lupus anticoagulant testing may be falsely positive and clot-based protein C and S testing may give spurious results.[30] Discussion with a haematologist before ordering these tests is recommended.

Conclusion

Direct oral anticoagulants are the first-line treatment for both initial and extended treatment of venous thromboembolism in most patients. An initial three months of anticoagulation is usually indicated for acute venous thromboembolism. After this, the decision of whether or not to continue anticoagulation indefinitely is made based on the likelihood of recurrence and the patient's bleeding risk. The favourable efficacy and safety of low-dose rivaroxaban and apixaban has expanded the indications for indefinite therapy. However, no anticoagulant is without risk and ongoing reassessment of the benefits of therapy versus the risk of bleeding is essential. ≺

Harry Gibbs has received honoraria from Pfizer Australia and Bayer for attending advisory boards and for presenting at educational meetings.

Huyen Tran has participated in advisory board meetings for Bayer.

Table 2 **Risk factors for venous thromboembolism recurrence**

Category	Example	Recurrence rate at 12 months*
Surgically provoked	Major surgery	Low (1%)
Distal deep vein thrombosis		Low (1–3%)
Non-surgically provoked	Long-distance air travel, hospitalisation for medical illness, oestrogen use	Intermediate (5%)
Unprovoked	No identified provoking factor	Intermediate (8–10%)
Persistent risk factor(s)	Active cancer, inflammatory bowel disease, antiphospholipid antibody syndrome	High (>10%)
Previous venous thromboembolism		High (15%)

* 12-month recurrence rate without anticoagulant therapy, after an initial anticoagulant course of 3–6 months.

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ARTICLE

Blood pressure: at what level is treatment worthwhile?

SUMMARY

High blood pressure is a key modifiable risk factor for cardiovascular events. A cardiovascular risk-based approach is best for determining when to start antihypertensive treatment.

Recent trial evidence has suggested lower blood pressure targets are beneficial. This has influenced international guidelines. The US guidelines have a lower threshold for defining hypertension than current Australian and European guidelines.

The patient's individual circumstances must be considered when treatment targets are set. For someone with a high risk of cardiovascular events, a systolic blood pressure target of 120 mmHg may be appropriate.

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antihypertensive drugs, blood pressure, cardiovascular risk, hypertension

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Introduction

High blood pressure is one of the key modifiable risk factors for adverse cardiovascular outcomes such as heart attack and stroke. Lifestyle changes including a healthy diet, quitting smoking, and increasing exercise are effective at reducing blood pressure. However many people will require antihypertensive drugs to reduce their blood pressure.

There has been much debate about the interpretation of observational data describing the relationship between blood pressure and cardiovascular outcomes. Studies of low-risk individuals reported log-linear relationships between systolic blood pressure and cardiovascular events down to the lowest levels for which adequate data were available (about 115 mmHg).[1] Meanwhile other studies included people at a higher risk of cardiovascular events, where many or even all had existing cardiovascular disease. These studies found that the lowest risk was at about 130–140 mmHg systolic, but suggested that blood pressure below this range was associated with a higher cardiovascular risk. This is the so-called J-curve.[2]

The challenge in interpreting these data is that they are likely to be confounded by reverse causality. This is when cardiovascular disease causes both lower blood pressure and a high risk of cardiovascular events and death, but the blood pressure level itself is not necessarily responsible for the higher risk of death.

Treatment targets in hypertension

Several large trials have randomised participants to different targets for systolic blood pressure. The most recent is the Systolic Blood Pressure Intervention Trial (SPRINT), where 9361 people at high cardiovascular risk, but without diabetes, were randomised to systolic targets of <120 mmHg (intensive treatment) or <140 mmHg (standard treatment).[3] The trial was stopped early (mean follow-up 3.3 years) due to a clear reduction of cardiovascular events in the intensive treatment arm (hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.64–0.89) as well as reduced all-cause mortality (HR 0.73, 95% CI 0.60–0.90).

Previous trials had suggested similar effects but may have been underpowered. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial all 10,251 participants were randomised to more or less intensive control of blood glucose and then 4733 participants went into the blood pressure trial (blood pressure targets <120 mmHg vs <140 mmHg).[4,5] However, a lower than anticipated event rate and shorter follow-up left the trial underpowered and there was no statistically significant difference between arms in event rates (HR 0.88, 95% CI 0.73–1.06). The glucose arm may have confounded the results as intensive glucose control increased the risk of cardiovascular and total mortality.[6] Long-term follow-up revealed statistically significant benefits for lower blood pressure targets in the patients randomised to standard glucose control (HR 0.75, 95% CI 0.60–0.95).[7]

The third Stroke Prevention Study (SPS3) compared systolic blood pressure targets (130–149 mmHg vs <130 mmHg) in 3020 people with a history of recent lacunar stroke. There was no statistically significant effect on stroke (HR 0.81, 95% CI 0.64–1.03), or the composite end point of myocardial infarction, stroke and cardiovascular death (HR 0.84, 95% CI 0.68–1.04), but intracerebral haemorrhage was significantly reduced (HR 0.37, 95% CI 0.15–0.95) with intensive blood pressure lowering.[8] Again, this trial experienced lower event rates than anticipated in the statistical

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power calculations, possibly meaning that it might have missed a real benefit.

A systematic review assessed all the evidence of more versus less intensive blood pressure lowering.[9] The meta-analysis of 20 trials found significant benefits for more intensive treatment on major cardiovascular events (relative risk 0.85, 95% CI 0.78–0.94)[10] which were generalisable across a variety of patient populations.[11] There was a small but statistically significant difference in severe hypotension with intensive treatment (0.3% vs 0.1% per person-year follow-up), but no statistically significant difference in severe adverse events associated with blood pressure lowering, dizziness or adverse events leading to discontinuation of treatment.[9]

Taken together, the evidence suggests that aiming for a target blood pressure of 120/80 mmHg will lead to a lower risk of cardiovascular events compared to a target of 140/90 mmHg among high-risk individuals. There is a small increase in the risk of adverse events with a lower target. These data can be used to inform patients so that they can make relevant decisions about the intensity of blood pressure lowering they would prefer.

What the guidelines say

There are Australian and international guidelines for the treatment of hypertension (see Table).[12-14] The Australian National Heart Foundation guidelines were already out for public consultation when the SPRINT results were published. Incorporation of these results into the guidelines happened late,[12] and with cautious interpretation of the results.

International guidelines including those in the USA (ACC/AHA guidelines)[13] and Canada[15] were revised with lower thresholds for starting treatment and lower treatment targets. The guidelines of the American College of Physicians and the American Academy for Family Physicians are an exception. They recommend starting treatment at 150 mmHg and with targets below 150/90 mmHg for people aged 60 years and older.[16]

The ACC/AHA guidelines[13] have a lower threshold for defining hypertension than the current Australian[12] and European[14] guidelines. The Australian and European guidelines are similar on when to start therapy, but Australia has lower treatment targets.

Controversies concerning recent recommendations

A source of contention in interpreting the SPRINT results is understanding how unattended automated measurement of blood pressure relates to usual practice. SPRINT used an average of three measures, one minute apart, after five minutes of unattended rest but the protocol did not specify that the study staff remain out of the room after the rest period,[17] so it may not have been entirely unattended. The Australian guidelines also recommend three measurements are taken after 'several minutes' rest with an average of the last two measures taken. For cardiovascular risk equations, measurements taken in the clinic should be used as this is what was used to derive the equations.[12] The Australian guidelines suggest using a mercury sphygmomanometer or automated digital device, noting mercury is being phased out of clinical use.[12] Use of an automated device has a demonstrated

Table **Comparison of international guidelines for the treatment of hypertension**

	Australia 2016[12]		USA 2017[13]		Europe 2018[14]	
Hypertension definition (mmHg)	**≥140/90**		**≥130/80**		**≥140/90**	
	Start treatment	**Treatment target**	**Start treatment**	**Treatment target**	**Start treatment**	**Treatment target**
General population	≥160/100*	<140/90	≥140/90	<130/80	≥160/90*	<130/80
High cardiovascular risk	≥140/90	<120/–	≥130/80	<130/80	≥140/90†	<130/80
Older age‡	–	<120/–	≥130/–	<130/–	≥140/90 Age 80+ 160/90	<130/80
Diabetes	≥140/90	<120/90	≥130/80	<130/80	≥140/90	<130/80
Kidney disease	≥140/90	<120/90	≥130/80	<130/80	≥140/90	<140/80

* For those with a systolic blood pressure of 140–159 mmHg treatment may begin after a period of lifestyle advice.
† Treatment may be considered in those with coronary disease or stroke with a systolic blood pressure of 130–140 mmHg.
‡ Older people are ≥75 years in Australian guidelines, ≥65 years in US guidelines, while the European guidelines include separate recommendations for 65–79 years and ≥80 years.

reduction in digit preference, and improved accuracy of recordings in Australian primary care.[18] A recent study has shown auscultatory, attended automated, and unattended automated blood pressure measurements conducted by general practitioners are comparable. The impact of this different measurement protocol may therefore be clinically minor.[19]

There are concerns about the potential harm from more people starting treatment at lower blood pressures.[20] The common adverse effects of antihypertensive therapy can be grouped two ways:

- effects of the particular drug chosen (e.g. cough associated with ACE inhibitors)
- effects of blood pressure lowering (often hypotension and syncope).

Concerns have been raised about renal safety due to the statistically significant difference in participants without chronic kidney disease experiencing at least a 30% reduction in estimated glomerular filtration rate (eGFR) in SPRINT.[3] However this measure is not a clinically meaningful outcome in people with eGFR above 60 mL/min/1.73 m^2. For those with chronic kidney disease, there was no significant difference in the composite renal outcomes, but there was insufficient power to determine if there was any effect on long-term dialysis.

The systematic review revealed no significant differences in severe adverse events associated with blood pressure lowering, dizziness or adverse events leading to discontinuation of more intensive blood pressure lowering therapy. However, there was a small difference in severe hypotension.[9]

Are Australians being undertreated or are Americans being over treated?

Australians could probably benefit from earlier treatment if they have a high cardiovascular risk. Australian guidelines start treatment at a higher threshold and involve a slower process of treatment escalation, but have lower treatment targets than the USA. The evidence suggests starting treatment at a lower level and aiming for a lower target will prevent more heart attacks, strokes and premature deaths from cardiovascular causes. Treatment individualisation based on absolute risk, tolerance, safety and efficacy should guide treatment decisions. Take into account patient characteristics, including how they value the potential harms and benefits.

At what level is treatment worthwhile?

A cardiovascular risk-based approach is best for determining when to begin treatment for lowering blood pressure (see the Australian absolute cardiovascular disease risk calculator). Many cardiovascular events happen in people with blood pressure below 140 mmHg and at high cardiovascular risk, or with existing cardiovascular disease.[21] The benefits for treating individuals at high cardiovascular risk may be substantial, down to a systolic blood pressure of 120 mmHg. For example, if someone has a systolic blood pressure of 130–140 mmHg and is at high risk of a cardiovascular event (>15% over five years) then treatment is likely to be worthwhile.

Important considerations include other conditions that further add to cardiovascular risk. These may not be adequately accounted for in existing risk equations. Examples include atrial fibrillation, obesity, socioeconomic deprivation, chronic kidney disease, and a history of high blood pressure during pregnancy.

Consider the person's treatment preferences, occupation, lifestyle and risk aversion when determining when to start treatment. Patients should choose the blood pressure target that gives them the best combination of cardiovascular benefit and tolerability. This is likely to vary substantially between individuals. Discuss the importance of adherence to the chosen treatment and the options available to aid adherence.

Conclusion

Treatment for lowering blood pressure is worthwhile in those at high risk of a cardiovascular event (>15% in 5 years). Aiming for a target systolic blood pressure below 120 mmHg can ensure maximal cardiovascular risk reduction if the treatment is tolerated and is appropriate for the individual patient. <

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ARTICLE

Meningococcal vaccines in Australia: a 2019 update

SUMMARY

Invasive meningococcal disease is a rare but serious infection caused by *Neisseria meningitidis*.

Serogroup B was the predominant serogroup causing invasive meningococcal disease in Australia until 2015. Serogroup W disease has increased substantially since 2014, and in 2017, serogroups B and W caused similar numbers of invasive disease cases.

Vaccines against serogroups A, C, W, Y and B are available for anyone who wishes to reduce the risk of meningococcal disease.

Vaccination is strongly recommended for people in high-risk age or population groups. These are children under 2 years, 15–19 year olds, Aboriginal and Torres Strait Islander children, and people with medical, occupational, behavioural or travel-related risk factors for invasive meningococcal disease.

Meningococcal ACWY vaccine is funded under the National Immunisation Program for babies aged 12 months. Since April 2019, it has been funded for year 10 students through a school program. There are additional state and territory-based programs for both meningococcal ACWY and meningococcal B vaccines.

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Introduction

Neisseria meningitidis is normally a commensal of the nasopharynx. However, it has the potential to invade the mucosa and cause invasive meningococcal disease, which most commonly presents as meningitis, septicaemia or both. There are 13 serogroups of *N. meningitidis*. Groups A, B, C, W_{135}, Y and X cause the majority of disease.[1]

Transmission occurs via large-droplet spread or direct contact with oral secretions. Carriage rates vary by population worldwide and by age. Asymptomatic carriage is most common in adolescents and young adults.[2] The incidence of invasive disease is highest in 0–4 year olds, especially infants, with a secondary peak in late adolescence and young adults. Invasive meningococcal disease is more common in Aboriginal and Torres Strait Islander children.

Risk factors

Risk factors for invasive disease include immune deficiencies such as asplenia, complement deficiencies and haemoglobinopathies, smoking, living in close quarters with other people, occupational exposure to *N. meningitidis*, and travel to highly endemic countries.

Incidence of disease

The incidence of invasive disease in Australia remains low, but has been increasing in recent years, with significant shifts in serogroup predominance as shown in the Figure. Universal meningococcal C vaccination was introduced to the National Immunisation Program in 2003 and resulted in a 94% reduction in serogroup C disease by 2017. Serogroup B has been the dominant serogroup in Australia for two decades, although its incidence has declined naturally in recent years even before the availability of meningococcal B vaccines.[3] Since 2014, serogroups W and Y have caused increased cases of invasive disease.

Meningococcal vaccines and recommendations

There are currently two groups of meningococcal vaccines available in Australia:

- conjugate vaccines for protection against serogroups A, C, W and Y
- recombinant protein-based vaccines for protection against serogroup B.

Conjugate vaccines against serogroup C alone remain available as catch-up vaccines, e.g. NeisVac-C and Menitorix (the Hib-MenC vaccine). Polysaccharide vaccines are no longer supplied or recommended for use in Australia.

Quadrivalent meningococcal (MenACWY) conjugate vaccines

Three quadrivalent conjugate vaccines against groups A, C, W and Y are currently available. They

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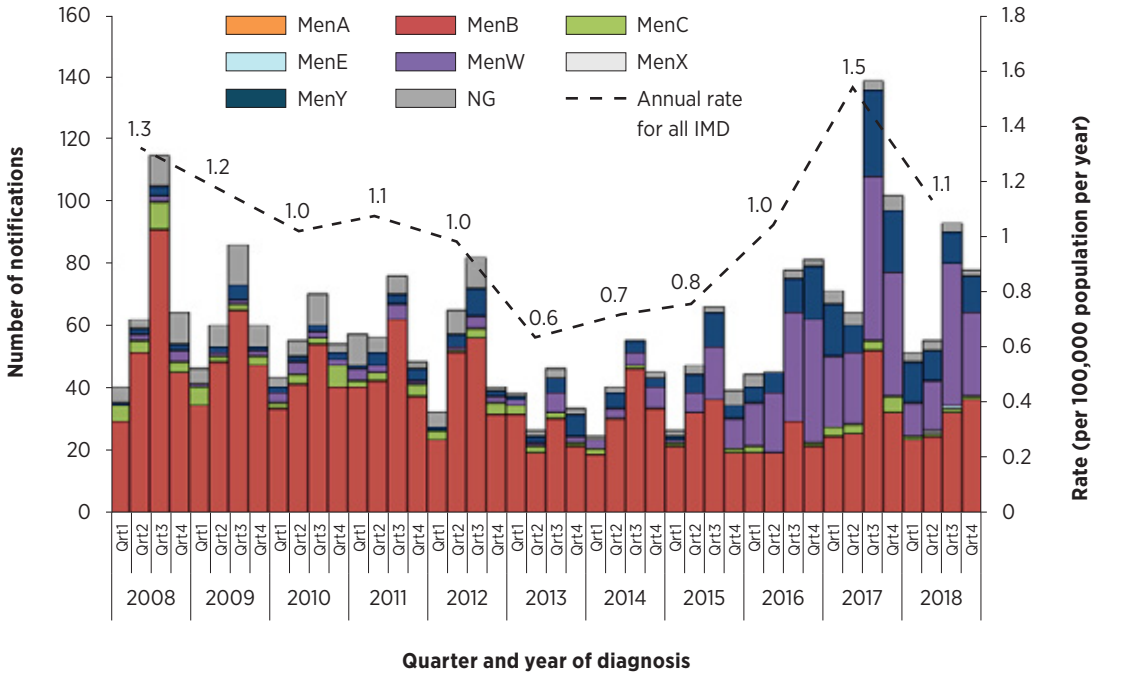
Fig. **Quarterly cases and annual rate of invasive meningococcal disease in Australia (1 January 2008 to 31 December 2018) by serogroup**



IMD invasive meningococcal disease
Men meningococcal serogroup
NG not groupable – includes meningococcal isolates that could not be identified, other isolates not grouped and where serogroup was not known
Q quarter
Source: www.health.gov.au/internet/main/publishing.nsf/Content/ohp-meningococcal-W.htm (accessed 2019 Jul 1)
Data extracted from National Notifiable Disease Surveillance System on 2019 Feb 1

contain capsular polysaccharide antigens conjugated to a protein carrier:

- Nimenrix – tetanus toxoid carrier
- Menveo – diphtheria CRM_{197} carrier
- Menactra – diphtheria toxoid carrier.

Indications and dosing schedules recommended by the Australian Technical Advisory Group on Immunisation vary by age and risk,[4] and are outlined in the Table. A single dose of Nimenrix is funded on the National Immunisation Program for babies aged 12 months. Since April 2019, year 10 students (aged 14–16 years) can receive the vaccine via a school-based program, with a catch-up dose available through general practice for 15–19 year olds who missed it at school. In recent years, individual states and territories have funded MenACWY vaccines for adolescents or provided them extensively, especially to high-risk age groups for control of outbreaks.

Nimenrix and Menveo induce a slightly better antibody level and persistence than Menactra in individuals over two years of age,[5,6] and are the preferred brands above this age.[4] For those who require more than one dose for the primary course, it is preferable to use the same brand. However, if it is unavailable, an alternate age-appropriate brand can be used to complete the course.

Protective effectiveness of MenACWY vaccines may decline over time. An observational study in the USA showed that among adolescents, the effectiveness of Menactra in adolescents against all serogroups was highest in the first year after vaccination (79%), but decreased to 61% after 3–8 years.[7] Revaccination of adolescents is safe, but is not routinely recommended in Australia.

MenACWY vaccines are well tolerated and severe adverse events are rare. They can be co-administered with other routine vaccines in the National Immunisation Program with one exception – Menactra should not be co-administered with the pneumococcal vaccine Prevenar 13, as this may reduce the immune response to some pneumococcal serotypes.[8] If they are both used, plan to give Prevenar 13 first, followed by Menactra at least four weeks later if possible. If Menactra and Prevenar 13 are inadvertently co-administered, a dose of Prevenar 13 should be repeated after an interval of at least eight weeks.[4]

Recombinant meningococcal B (MenB) vaccines

Two recombinant protein-based multicomponent vaccines against serogroup B disease are currently available:

- Bexsero (also called MenB-MC) – contains multiple recombinant protein components and outer membrane vesicles of a strain of serogroup B meningococcus
- Trumenba – contains two subfamilies of factor-H binding protein (fHBP).

Indications and dosing schedules by age are summarised in the Table. MenB vaccines are currently not funded on the National Immunisation Program, but are available by private prescription. In South Australia, they are available through a state-based program.

Given the low incidence of meningococcal B disease, vaccine efficacy in pre-approval studies was inferred from immune responses to the component antigens, rather than from clinical end points.

Bexsero (MenB-MC) can be used from age six weeks, according to the Australian Immunisation Handbook.[4] A meta-analysis of immunogenicity studies found that 92% of children and adolescents achieved seroconversion 30 days after the primary vaccination course. However the long-term immunogenicity against some strains was suboptimal.[9] Early effectiveness data from the UK, where universal MenB-MC vaccination was introduced in 2015, showed that a two-dose primary regimen was 82.9% effective (95% confidence interval 24.1–95.2) against all strains of meningococcal B in infants, observed up to 10 months after vaccination.[10] The cost-effectiveness of universal MenB-MC vaccination is affected by the country-specific incidence of meningococcal B disease.[11] The incidence in Australia is relatively low compared to countries that adopted universal vaccination, at 0.47 cases per 100 000 in 2015.[3]

Trumenba is registered for use from 10 years of age. Assessment of its clinical effectiveness is not yet available.

Bexsero and Trumenba are not interchangeable and the same brand must be used to complete the vaccination course. Bexsero contains four major antigens that are preserved across multiple species of *Neisseria*, and may provide some protection against other capsular groups. However the extent of clinically important cross-protection is not known.[12,13]

MenB vaccines can be co-administered with MenACWY vaccines as well as other routine vaccinations. Fever is a very common adverse event following administration of Bexsero in young children and is more likely if Bexsero is co-administered with other vaccines. This risk can be reduced by separating administration of Bexsero from other vaccines (e.g. by at least three days). Prophylactic paracetamol is recommended for all children under two years receiving Bexsero in Australia.[4]

Conclusion

Safe and effective vaccines are available for prevention of invasive meningococcal disease caused by the most dominant serogroups in Australia. Primary care immunisation service providers are important for facilitating widespread uptake of meningococcal vaccines. MenACWY vaccine is provided for children aged 12 months and adolescents under the National Immunisation Program.

The MenACWY and MenB vaccines are strongly recommended for individuals at increased risk of invasive meningococcal disease. However, only the MenACWY vaccine is recommended for people travelling to regions where serogroups A, C, W, or Y are endemic. Health professionals should look out for at-risk patients and discuss vaccination options with them. Meningococcal vaccination is available for anyone who would like to reduce the risk of invasive meningococcal disease. <

Conflict of interest: none declared

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Table **Meningococcal vaccine 2019 recommendations by age and risk group**

		Medically at risk				
Who should be vaccinated?		Those with medical risk factors for invasive meningococcal disease, including: • complement deficiencies • current or future treatment with eculizumab • haemoglobinopathies • haematopoietic stem cell transplant • functional/anatomical asplenia • people living with HIV				
Which vaccine(s) are recommended?		MenACWY MenB				
Which vaccine(s) are NIP funded?		Nil				
		6 weeks–5 months	**6–8 months**	**9–11 months**	**12–23 months**	**≥2 years**
MenACWY	**MenACWY dosing schedule by age at first dose**	4 doses Minimum 8-week intervals. 4th dose at 12 months of age or 8 weeks after 3rd dose, whichever is later	3 doses Minimum 8-week intervals. 3rd dose at 12 months of age or 8 weeks after 2nd dose, whichever is later	3 doses Minimum 8-week intervals. 3rd dose at 12 months of age or 8 weeks after 2nd dose, whichever is later	2 doses Minimum 8-week interval	2 doses Minimum 8-week interval
	Preferred brands (MenACWY)	Menveo or Nimenrix (Menactra not registered for use for this age group)		Menveo, Nimenrix or Menactra*		Menveo or Nimenrix preferred to Menactra*
	Further MenACWY booster doses required?	Yes, if ongoing increased risk of invasive meningococcal disease If age ≤6 when completed initial MenACWY vaccination course, give MenACWY booster 3 years after primary schedule, then every 5 years If age ≥7 when completed course, give MenACWY booster every 5 years				
		6 weeks–5 months	**6–11 months**	**12 months–9 years**	**≥10 years**	
MenB	**MenB dosing schedule by age at first dose**	Bexsero: 4 doses, minimum 8-week intervals, 4th dose at 12 months or 8 weeks after 3rd dose, whichever is later	Bexsero: 3 doses, minimum 8-week intervals, 3rd dose at 12 months or 8 weeks after 2nd dose, whichever is later	Bexsero: 2 doses, minimum 8-week interval	Bexsero: 2 doses, minimum 8-week interval Trumenba: 3 doses. Dose 2 should be ≥4 weeks after dose 1. Dose 3 ≥4 months after dose 2 and ≥6 months after dose 1	

* Menactra should not be co-administered with Prevenar 13
Men meningococcal serogroup
NIP National Immunisation Program
These data are summarised from the online Australian Immunisation Handbook, December 2018.[4]
An A3 single-page version of this table is available online.

FURTHER READING

National Centre for Immunisation Research and Surveillance. Meningococcal vaccines – FAQs. www.ncirs.org.au/ncirs-fact-sheets-faqs/meningococcal-vaccines-faqs [cited 2019 Jul 1]

National Centre for Immunisation Research and Surveillance. Meningococcal vaccines for Australians. Fact sheet April 2019. www.ncirs.org.au/ncirs-fact-sheets-faqs/meningococcal-vaccines-australians [cited 2019 Jul 1]

<table>
<tr><th colspan="5">Healthy individuals</th><th>Occupationally at risk</th><th>Travellers</th></tr>
<tr><td colspan="5">Anyone aged ≥6 weeks who wishes to reduce their risk of invasive meningococcal disease, and in particular the following high-risk demographics:
• infants aged <2 years
• adolescents aged 15–19 years
• Aboriginal and Torres Strait Islander children aged <15 years
• adults aged 20–24 years who live in close quarters (e.g. military, student accommodation)
• adults aged 20–24 years who smoke</td><td>E.g. laboratory workers who handle Neisseria meningitidis</td><td>Travellers aged ≥6 weeks travelling to a country endemic for meningococcal A, C, W or Y, as well as Hajj pilgrims</td></tr>
<tr><td colspan="5">• MenACWY
• MenB</td><td>MenACWY
MenB</td><td>MenACWY</td></tr>
<tr><td colspan="5">National Immunisation Program: Nimenrix (MenACWY) is funded at 12 months (GP) and at School Year 10 (14–16 years, school-based program), with catch-up for 15–19 year olds who have not received a dose previously (GP based).</td><td>Nil</td><td>Nil</td></tr>
<tr><th>6 weeks–5 months</th><th>6–8 months</th><th>9–11 months</th><th>12–23 months</th><th>≥2 years</th><th></th><th></th></tr>
<tr><td>3 doses
Minimum 8-week intervals
3rd dose at 12 months of age or 8 weeks after 2nd dose, whichever is later</td><td>2 doses
2nd dose at 12 months of age</td><td>2 doses
2nd dose at 12 months of age</td><td>Nimenrix: 1 dose
Menveo/ Menactra: 2 doses, 8 weeks apart</td><td>One dose</td><td>Dosing depends on presence of medical risk factors or not</td><td>Dosing depends on presence of medical risk factors or not</td></tr>
<tr><td colspan="2">Menveo or Nimenrix
(Menactra not registered for use for this age group)</td><td colspan="2">Menveo, Nimenrix or Menactra*</td><td>Menveo or Nimenrix preferred to Menactra*</td><td>Menveo or Nimenrix preferred to Menactra*</td></tr>
<tr><td colspan="5">No, not required</td><td>Yes, every 5 years</td><td>Yes, every 5 years if ongoing risk</td></tr>
<tr><th colspan="2">6 weeks–11 months</th><th>12 months–9 years</th><th colspan="2">≥10 years</th><th></th><th></th></tr>
<tr><td colspan="2">Bexsero: 3 doses
Minimum 8-week intervals, 3rd dose at 12 months or 8 weeks after 2nd dose, whichever is later</td><td>Bexsero: 2 doses
Minimum 8-week interval</td><td colspan="2">Bexsero: 2 doses, minimum 8-week interval
Trumenba: 2 doses, minimum 6-month interval</td><td>Dosing depends on presence of medical risk factors or not</td><td>MenB is not routinely recommended for travellers</td></tr>
</table>

* Menactra should not be co-administered with Prevenar 13
Men meningococcal serogroup
NIP National Immunisation Program
These data are summarised from the online Australian Immunisation Handbook, December 2018.[4]
An A3 single-page version of this table is available online.

ARTICLE

The safety of computerised prescribing in hospitals

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Keywords
computer-assisted drug therapy, decision support systems, electronic prescribing, medication errors

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SUMMARY

The implementation of computerised prescribing can result in large reductions in prescribing error rates. The flow-on effects to patient outcomes are not well studied.

The reduction in errors is dependent on prescribers becoming proficient in using the electronic prescribing system. All potential safety benefits are therefore not expected to be achieved immediately.

Electronic prescribing systems introduce new types of errors, most frequently errors in selection. Some of these errors can be prevented if the system is well designed.

Computerised decision support embedded in electronic prescribing systems has enormous potential to improve medication safety. However, current support systems have a limited capacity to provide context-relevant advice to prescribers.

Introduction

Although most general practices are now computerised,[1,2] Australia lags behind the USA in the adoption of electronic prescribing systems in hospitals.[3] The key benefits of electronic prescribing systems include improved legibility, improved availability (anywhere and anytime) and improved continuity of care, for example by having rapid access to a patient's medication list from a previous admission. A major benefit is reducing medication errors. However, electronic prescribing systems can introduce new errors.

Preventing medication errors

Medication errors are among the most frequently reported incidents in hospitals and a major patient safety priority. The World Health Organization has announced the third Global Patient Safety Challenge to be 'medication without harm'.[4] The Australian Commission on Safety and Quality in Health Care endorses the use of electronic prescribing systems for medication management in hospitals, suggesting that these programs can 'improve the safety and quality of health care'.[5] But do they?

There is now considerable evidence to show that medication errors in hospitals decline following the implementation of electronic prescribing systems.[6] The evidence includes an Australian-controlled before-and-after study of the introduction of two commercial electronic prescribing systems in two Sydney hospitals.[7] These interventions resulted in a large (>50%) reduction in prescribing error rates. Whether this sizeable reduction in medication error led to improved outcomes for patients is uncertain. Very few studies go beyond evaluating the effect of electronic prescribing systems on medication errors, although a large Australian trial is currently attempting to measure the impact of the systems on patient harm.[8]

Delayed benefits

There is no evidence to show whether or not the benefits of electronic prescribing systems on medication errors are immediate. Researchers typically avoid the treacherous 'shakedown' phase,[9] and wait for the use of electronic prescribing systems to become routine before measuring the post-implementation prescribing error rates.

Users of electronic prescribing systems describe the period immediately following implementation as risky, as prescribers attempt to navigate the unfamiliar, often unintuitive landscape that is computerised prescribing.[10] Even if familiar with prescribing in one system, using a different system requires new training and practice as systems differ considerably in display, features, functions and navigation. This is in contrast to using the standard National Inpatient Medication Chart.[11]

It is likely that the introduction of electronic prescribing systems results in a transient increase in prescribing errors, as users familiarise themselves with the system. This is followed by a substantial decline in errors (as reported in a large number of trials), once proficiency in computerised prescribing is achieved. Heightened vigilance and close monitoring of system use is therefore essential in the early stages of implementation, especially for the detection of unanticipated problems with the design of the system

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and its use or implementation, for example system glitches and gaps in training for prescribers.

New errors

Accompanying reports on the effectiveness of electronic prescribing systems is a growing body of evidence showing that these systems can introduce new types of errors.[12,13] In a study of electronic prescribing system errors in the USA, researchers identified 22 types of medication error risks that were facilitated by the electronic system.[13] These included errors such as doctors ordering drugs for the wrong patient, or using the wrong log-in, because the previous user had failed to log out of the system at the computer terminal.

These problems are not unique to the USA and evidence of electronic prescribing system-related errors in Australia is increasing. For example, in a survey of 664 users of electronic prescribing systems (doctors, nurses and pharmacists) in Victoria, 58% of respondents said that they thought the electronic system had introduced new types of error.[14] An audit of discharge medications at a tertiary Brisbane hospital found more errors in computer-generated prescriptions than paper-based prescriptions.[15] In the one large-scale Australian study to quantify the rate at which these system-related errors occur, approximately 42% of prescribing errors were related to the use of an electronic prescribing system – that is 78 system-related errors per 100 patient admissions.[16]

The most frequent type of error was selection error, where prescribers made the wrong selection from a drop-down menu. An interesting result was that, although the study was undertaken at two hospitals, each using a different electronic prescribing system, the overall rate of system-related errors was equivalent at both sites. However, selection errors were four times more likely in one hospital than the other. This reflected differences in the design of the systems (as one system required doctors to make many more selections from drop-down menus).

The design of electronic prescribing systems is important in preventing, or facilitating, prescribing errors. Placing the most frequently used items at the top of a drop-down menu is likely to minimise selection errors, as is limiting the number of options on a list.[16,17] In a study that explored the use of lists of antibiotic orders in an electronic prescribing system, a doctor said 'Sometimes there are a lot of options…I know my colleagues have accidentally clicked the wrong dose just because there are a million different regimens or dosages'.[18] As expected, the more choices a user is presented with, the longer they take to make a selection (the Hick-Hyman Law[19]). This is an important rule to keep in mind when designing systems for use on a busy hospital ward. The result of presenting too many options in electronic prescribing systems is likely to be intentional mis-selection from a list, with users choosing the first option on a menu to save time.

Decision support

Despite the emergence of new types of errors, research has shown that computerised prescribing eliminates many more errors than it creates.[15] One of the fundamental components of electronic prescribing, perceived to be critical to achieving the anticipated benefits of improved safety and quality, is computerised decision support.

Common forms of computerised decision support include alerts and reminders, pre-written orders and order sets, calculators, and access to online reference material.[20,21] However, decision support is also implicit in the design of electronic prescribing systems. For example, limiting the options on a drop-down menu to doses that are appropriate for a drug can prevent a dose 10 times larger than intended being prescribed. Preventing prescribers from ordering a drug unless a patient's allergies (or 'no allergy') are entered into the electronic prescribing system, can avoid a patient receiving a drug to which they are allergic.

Problems

Although the potential of computerised decision support is enormous, the enthusiasm for what is possible has overshadowed a careful consideration of the users and the environment in which they work. In many cases, the result has been a significant misalignment of computerised decision support and prescriber workflow. Alert fatigue, an inevitable consequence of too many alerts being presented, is an established and enduring problem for prescribers.[22] Automation bias, a user's over-reliance on the system to detect errors ('the system did not alert me, so the prescription is OK'), is also a risk for prescribers.[23]

Not all computerised decision support integrates well with hospital clinical information systems, and current computerised decision support systems are unlikely to capture all types of errors. In taking a closer look at the types of prescribing errors that declined following the implementation of electronic prescribing in two Australian hospitals, the majority of the decline was in procedural errors such as incomplete and illegible orders.[7] The computerised systems were not as effective in targeting clinical errors, such as the wrong doses and wrong drugs, which are the types of error that could be prevented by well-designed computerised decision support.

Different electronic prescribing systems (and different configurations of the same electronic prescribing

systems) include varying levels and types of computerised decision support.[7] This is the case even for the same types of decision support. For example, there is no standardised list of drug–drug interaction alerts to include in a system or a standardised way to present information in an alert, resulting in high variability across systems.[24] This is despite users being fairly consistent in their preferences for how alert information should be displayed.[25] Variability is particularly challenging for prescribers who work across multiple sites or organisations. Inconsistencies between electronic prescribing systems are something prescribers should keep in mind. User training should include clear information about the computerised decision support capabilities of the particular system the prescribers will be using.

Solutions

For computerised decision support to reach its full potential, smarter programs are needed. These would not assume that all patients are non-geriatric (or all are geriatric) and have normal physiological function. Computerised decision support should be context-aware to trigger alerts only when relevant for a particular patient (age, renal function) and when a particular drug form, dose, or frequency is prescribed. Although trials of smart computerised decision support have begun to emerge in the USA,[26,27] Australia is not quite there yet.

Conclusion

There is now little doubt that computerised prescribing reduces medication errors in hospitals. However, it also introduces new types of errors. Well-designed systems that provide context-relevant information to prescribers are likely to result in the largest benefits to users and patients. ◀

Conflict of interest: none declared

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MEDICINAL MISHAP

Iatrogenic Cushing's syndrome with inhaled fluticasone

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Case 1

A 52-year-old female with HIV and allergic bronchopulmonary aspergillosis had been taking co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, itraconazole and inhaled fluticasone furoate/vilanterol for many months. When she developed a respiratory tract infection she was prescribed amoxicillin/clavulanic acid and subsequently erythromycin.

The patient was referred with facial swelling and she was noted to have developed moon facies and vocal hoarseness. On examination there was proximal myopathy, skin thinning with bruising, a small buffalo hump, and a blood pressure of 200/90 mmHg. Investigations revealed a low morning cortisol of 37 nmol/L (reference range (RR) 150–520 nmol/L).

Case 2

A 65-year-old male with a history of smoking-related chronic obstructive pulmonary disease was treated with inhaled fluticasone furoate/vilanterol. He also had HIV and was commenced on elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide which was well tolerated when he was followed up after one month.

Five months later, the patient reported fatigue, mood changes, facial puffiness, development of a buffalo hump, and weight gain. Proximal myopathy was noted on examination. There was a low serum cortisol of 14 nmol/L (RR 100–400 nmol/L).

Comment

These two cases illustrate the potential for iatrogenic Cushing's syndrome to result from drug interactions with inhaled corticosteroids. During 1971–2017, 24 cases were reported to the Therapeutic Goods Administration relating to fluticasone and nine relating to budesonide.[1] Most of these cases involved co-administration with itraconazole and ritonavir.[2,3]

Most of the dose of an inhaled corticosteroid remains in the oropharynx, but a proportion is swallowed and a smaller proportion remains bioactive after extensive first-pass metabolism by the liver. Both fluticasone and other corticosteroids require metabolism by the cytochrome P450 (CYP) 3A4 enzyme for inactivation and elimination.[2] The potency of inhaled corticosteroids also differs. These cases involved fluticasone furoate, a formulation approximately five times more potent than fluticasone propionate.

Potent inhibitors of CYP3A4 include itraconazole and the antiretroviral 'boosters' such as ritonavir and cobicistat, along with many other drugs such as erythromycin.[4] Itraconazole inhibits the fungal cytochrome system, with a collateral impact on human cytochromes including CYP3A4. HIV 'boosters' increase the bioavailability of other anti-HIV drugs, but also affect fluticasone and other drugs metabolised by CYP3A4.

Appropriate management of iatrogenic Cushing's syndrome includes glucocorticoid replacement for adrenal suppression and screening for, and prevention and management of, common comorbidities associated with glucocorticosteroid excess (such as dyslipidaemia, osteoporosis, diabetes and hypertension). Optimally the risk of this adverse effect could be reduced by either lowering the dose or frequency of the inhaled corticosteroid, selecting a less potent corticosteroid, or selecting alternatives for the azole antifungal or the 'booster' HIV drugs that do not inhibit CYP3A4.

To minimise systemic absorption, patients should be educated when using inhaled corticosteroids to rinse with water, gargle and spit out after use. The potential interaction of inhaled fluticasone and CYP3A4 inhibitors has been known for some time. These two recent cases are a timely reminder for clinicians to pay attention to inhaled corticosteroids, especially fluticasone, when taking a medication history and when prescribing potent cytochrome inhibitors such as the azole antifungals and particular antiretrovirals.

Conclusion

- Inhaled corticosteroids are metabolised by CYP3A4.
- Inhaled corticosteroids can cause Cushing's syndrome when co-administered with CYP3A4 inhibitors.
- Significant inhibitors of CYP3A4 include itraconazole, the HIV 'boosters' ritonavir and cobicistat, and erythromycin.
- Strategies to minimise these interactions include patient education, careful selection and dosing of the inhaled corticosteroid, and choice of antifungal drugs, as well as selecting non-interacting antiviral drugs.

Conflict of interest: none declared

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New drugs

Inotuzumab ozogamicin

Approved indication: acute lymphoblastic leukaemia

Besponsa (Pfizer)
vials containing 1 mg powder for reconstitution
Australian Medicines Handbook section 14.2, Non-cytotoxic antineoplastics

Chemotherapy induces a complete remission in 60–90% of people with newly diagnosed acute lymphoblastic leukaemia. However, most of these patients will relapse. For those who relapse after chemotherapy or do not respond, the aim of subsequent treatment is complete or almost complete remission. This then allows them to have a stem cell transplant which is potentially curative.

Treatment options for these patients include:

- chemotherapy
- a tyrosine kinase inhibitor (e.g. imatinib, dasatinib or ponatinib) for those with Philadelphia chromosome (Ph)-positive disease
- blinatumomab (an anti-CD3/CD19 antibody) for those with Ph-negative disease.

Inotuzumab ozogamicin is the second immunotherapy after blinatumomab to be approved for adults with refractory or relapsed acute lymphoblastic leukaemia. This drug is a humanised monoclonal antibody specific for CD22 glycoprotein (present on most B-cell blasts) which is conjugated to a cytotoxic drug called calicheamicin. It works by binding to CD22 on cells where it is internalised. Once inside, calicheamicin is released and causes breaks in double-stranded DNA which leads to apoptosis.

Inotuzumab ozogamicin has been compared to standard chemotherapy in an open-label, phase III trial (INO-VATE) of patients with CD22-positive, Ph-positive or -negative, relapsed or refractory disease. To be eligible, they had to have at least 5% bone marrow blasts and have previously received 1–2 chemotherapy regimens.[1] In total, 326 participants were randomised 1:1 to the study drug or a standard chemotherapy regimen. Inotuzumab ozogamicin (1.8 mg/m^2/cycle) was given intravenously in three divided doses on days 1, 8 and 15 of a cycle. The first cycle lasted 21 days and subsequent cycles were 28 days. The INO-VATE study continued for two years after the last patient was randomised. Patients were treated for up to six cycles.[2]

Patients received a median of three treatment cycles of inotuzumab ozogamicin and one cycle of standard chemotherapy. In a remission analysis of 218 patients, complete or almost complete remissions (i.e. without haematologic recovery) were significantly more likely with the study drug than with standard chemotherapy (80.7% vs 29.4% of patients), except in patients carrying the Ph-positive or t(4;11) genetic abnormalities.[1] In an intention-to-treat analysis of all 326 patients, progression-free survival was significantly longer with inotuzumab ozogamicin than with chemotherapy (5 vs 1.8 months), however overall survival was only one month longer (7.7 vs 6.7 months) (see Table).[1] Two years after the start of treatment, overall survival rates with inotuzumab ozogamicin were 22.8% compared with 10% with standard chemotherapy.[2]

In a two-year safety cohort of 164 patients who took the study drug, the most common serious treatment-emergent adverse events were veno-occlusive liver disease (14%), febrile neutropenia (11.6%), pneumonia (6.1%), disease progression (4.9%), fever (3%), sepsis (2.4%), neutropenic sepsis (1.8%), septic shock (1.8%) and respiratory failure (1.2%).[2]

Table **Efficacy of inotuzumab ozogamicin in adults with refractory or relapsed acute lymphoblastic leukaemia**

Treatment	Complete or almost complete remission*	Median progression-free survival	Median overall survival
Inotuzumab ozogamicin	80.7%	5 months	7.7 months
Standard chemotherapy	29.4%	1.8 months	6.7 months

* Almost complete remission was complete remission with incomplete haematologic recovery defined as less than 1000 neutrophils/microlitre, less than 100,000 platelets/microlitre, or both.

Source: Reference 1

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Some of the views expressed in the following notes 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.

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NEW DRUGS

More patients went on to have a stem cell transplant after antibody conjugate treatment than after standard chemotherapy (48% vs 22%).[2] However, the post-transplant non-relapse mortality rate was higher with the study drug than with chemotherapy (39%, 31/79 vs 23%, 8/35). This was partly due to five fatal cases of veno-occlusive liver disease in the inotuzumab ozogamicin group.[2]

Because of the serious hepatotoxicity with this drug, it is contraindicated in anyone who has had previous veno-occlusive liver disease or ongoing liver disease such as cirrhosis or hepatitis. Liver enzymes should be checked before and after every dose as dose adjustment or discontinuation may be indicated. Liver enzymes should also be closely monitored for the first month after stem cell transplantation. Prescribers should be aware that older age and previous stem cell transplantation may increase the risk of hepatotoxicity.

There have been no clinical drug interaction studies with inotuzumab ozogamicin. QT prolongation has been reported so, if concurrent use of other drugs with the same effect cannot be avoided, an electrocardiogram and assessment of electrolytes are advisable before starting treatment.

This drug should be given intravenously over one hour. Infusion-related reactions are common after the first treatment cycle so a corticosteroid, antipyretic and antihistamine are recommended before each dose is given.

Inotuzumab ozogamicin was significantly better at inducing complete or almost complete remission than standard chemotherapy in people with relapsed acute lymphoblastic leukaemia, except for those carrying the Philadelphia chromosome or the t(4;11) mutation. In people who went on to have a stem cell transplant, a quarter developed hepatic veno-occlusive disease which was fatal in five of 18 cases.

Patients can expect to survive a median of 7.7 months with inotuzumab ozogamicin, which is only one month longer than with chemotherapy. It is unclear if inotuzumab ozogamicin will be better than blinatumomab for people with Ph-negative disease as there have been no head-to-head trials. However, when blinatumomab was compared to chemotherapy in similar patients, they also survived for 7.7 months.[3]

T manufacturer provided the product information

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

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

Peramivir

Aust Prescr 2019;42:143
https://doi.org/10.18773/austprescr.2019.047
First published 17 June 2019

Approved indication: influenza

Rapivab (Seqirus)
vials containing 200 mg/20 mL for dilution
Australian Medicines Handbook section 5.3.2, Neuraminidase inhibitors

Neuraminidase inhibitors can be used in the treatment of influenza. They prevent the release of the virus from infected cells.[1] Peramivir is a neuraminidase inhibitor that has a higher affinity for the influenza virus than oseltamivir. It was given an emergency use authorisation in the USA during the H_1N_1 pandemic of 2009.

Unlike oseltamivir, peramivir is given by intravenous infusion. The drug must be diluted then infused over 15–30 minutes. Only a single dose is required. This has a half-life of 20 hours with most of the dose being excreted unchanged in the urine. A lower dose is recommended for patients with a creatinine clearance below 50 mL/minute.

There have been several studies of peramivir for the treatment of influenza. One of the studies used to support the Australian authorisation of peramivir was a Japanese double-blind, placebo-controlled trial. This studied 300 adults who had developed flu-like symptoms within the previous 48 hours. The clinical diagnosis of influenza was confirmed with a rapid antigen test. Nearly all the patients were infected with influenza A subtypes. For the patients randomised to the placebo group, their symptoms resolved in a median of 81.8 hours. Symptoms were alleviated significantly sooner with intravenous peramivir. They resolved in a median of 59.1 hours with a dose of 300 mg and in 59.9 hours with a dose of 600 mg.[2]

Another Asian study has compared these single doses of peramivir with a five-day course of oseltamivir 75 mg twice daily. This double-blind trial randomised 1099 adults within 48 hours of developing influenza, confirmed by rapid antigen testing. Most of the patients were infected with influenza A subtypes. Their symptoms were alleviated in a median of 78 hours with 300 mg peramivir, 81 hours with 600 mg peramivir and 81.8 hours with oseltamivir.[3]

Peramivir is also being compared with oseltamivir in children with influenza. Preliminary results have been published for 85 patients treated with peramivir and 23 given oseltamivir. The symptoms of influenza were alleviated in a median of 75.6 hours with peramivir and 99.8 hours with oseltamivir.[4]

Safety data are available from 2155 patients treated with peramivir. The infusion is generally well tolerated with the most common adverse effects being gastrointestinal, particularly diarrhoea.[2,3] In the comparative trial 10–11% of the patients given peramivir had a decreased neutrophil count compared with 9.3% of the oseltamivir group.[3] Glucose and liver enzymes may increase. Overseas postmarketing data have included rare reports of anaphylaxis, and severe skin rashes. Neuropsychiatric events have also been reported.

The usefulness of neuraminidase inhibitors is limited by the need to give them within 48 hours of symptoms developing. In otherwise healthy people an infusion of peramivir will alleviate symptoms about a day faster than placebo.[2] Its efficacy is similar to oral oseltamivir, but it may reduce fever more rapidly in adults.[3] There is insufficient evidence to show that peramivir is effective for serious cases of influenza requiring hospitalisation. Its efficacy and safety in pregnancy are also unknown. Although the 300 mg dose had similar efficacy, the recommended adult dose is 600 mg as the higher dose reduces viral shedding. As with other neuraminidase inhibitors, the influenza virus may develop resistance to peramivir.

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.

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Correction

Prescribing for transgender patients [Correction]

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The article on prescribing for transgender patients (Aust Prescr 2019;42:10-3) has been corrected.

In the second paragraph of the 'Monitoring' section, the target estradiol level for transwomen on treatment should be 400–700 pmol/L (not 400–700 mmol/L).

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