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EDITORIAL

Elimination of hepatitis C in Australia by 2030: a decade and counting

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direct-acting antiviral drugs, hepatitis C, hepatocellular carcinoma, liver disease

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Direct-acting antiviral therapy for chronic hepatitis C virus infection is one of the great advances in clinical medicine in recent decades.[1] Several regimens have been licensed since 2014 which allow simple, once-daily oral dosing for 8–12 weeks. These regimens have proved to be tolerable and highly efficacious (cure rates of >95%). The listing of direct-acting antiviral regimens on the Pharmaceutical Benefits Scheme (PBS) from March 2016 has transformed the management of hepatitis C in Australia and has provided optimism for the elimination of hepatitis C virus.

The World Health Organization (WHO) has developed ambitious targets for hepatitis C virus elimination by 2030. These include:

- improving primary prevention e.g. safe injections in healthcare settings and for people who inject drugs
- upscaling screening for hepatitis C and linkage to care, enabling treatment for 80% of those with chronic hepatitis C
- lowering the impact of disease, including a 65% reduction in hepatitis C-related deaths and a 90% reduction in new infections.[2]

In 2018, 12 countries were considered 'on-track' to achieve the WHO elimination targets. These include several high-income countries – Australia, France, Iceland, Italy, Japan, South Korea, Spain, Switzerland, United Kingdom – and three low–middle income countries – Egypt, Georgia, Mongolia.

Of an estimated 188,000 people in Australia with chronic hepatitis C, around 85,000 had been treated with direct-acting antiviral therapy by the end of 2019. Importantly, uptake was comparable, if not higher, among high-risk populations including people who currently inject drugs and HIV-infected gay and bisexual men, compared to low-risk populations.[3] Within the broader population of former and current injecting drug users, evidence from a large New South Wales data linkage study indicates that those who are currently drug dependent (i.e. taking opioid agonist therapy such as methadone or buprenorphine or in hospital for a drug-related cause) have a higher uptake than those who are not currently drug dependent.[4]

The rapid uptake of direct-acting antiviral therapy has translated into around a 30% reduction in deaths from liver problems related to hepatitis C since 2015 and a plateauing of hepatitis C-related hepatocellular carcinoma cases.[5] This is following a steady rise in these cases and deaths over the previous decade. These trends indicate a high uptake of therapy in people with more advanced liver disease. There is also evidence of a declining incidence of hepatitis C among high-risk populations, including downward trends in new infections in younger age groups. This is consistent with a probable benefit from hepatitis C 'treatment as prevention'.[6]

Australia is an international leader in its shift to managing hepatitis C in primary care and drug and alcohol services, with most people now prescribed therapy by non-specialists. There is, however, much more to do, particularly given the continued decline in people treated per year (from more than 32,000 in 2016 to around 11,500 in 2019).

Although more than 6000 GPs have prescribed direct-acting antiviral therapy, most have only prescribed it for one or two patients. Further research needs to be undertaken to understand if this low prescribing is related to suboptimal hepatitis C screening, barriers to prescribing, or low caseloads.

GPs clearly have a key role in increasing testing for hepatitis C. Taking a non-judgemental approach, they should consider testing patients with elevated liver enzymes but no readily identifiable risk factors. Hepatitis C assessment and treatment monitoring have been simplified with the advent of well-tolerated, highly curative direct-acting antiviral therapy. However, key elements remain including staging of liver disease (hepatic elastography, shear-wave elastography, surrogate biomarkers), evaluation of potential drug–drug interactions and testing for HIV and chronic hepatitis B.

There are several strategies required to achieve hepatitis C virus elimination in Australia.

First, treatment assessment and delivery should continue to be simplified. The recent removal of mandatory pre-treatment genotype testing is an important first step given most patients are now being treated with pan-genotypic regimens (sofosbuvir/velpatasvir, glecaprevir/pibrentasvir). Further measures will include adoption of finger-prick-based rapid point-of-care hepatitis C RNA testing (result within 1 hour) or dried blood spot sample (sent to a laboratory) to confirm active infection, particularly in patients with difficult venous access. The extremely favourable safety profile of the pan-genotypic regimens means

that, unless there is evidence of cirrhosis, an RNA test before treatment is started and then three months after the end of treatment to assess for cure may be the only investigations required in the near future.

Second, monetary incentives for both practitioners to prescribe and patients to start therapy should be considered.

Third, hepatitis C virus screening (and potential treatment) needs to be integrated into settings with high-risk populations. These include prison entry, on admission to hospital for drug injecting-related conditions, and within drug and alcohol and mental health services.

Finally, primary prevention needs to be maintained and in some areas strengthened. For example, high rates of reinfection post treatment in prisons clearly indicates the need for more harm reduction, including expanded opioid agonist therapy and consideration of prison-based needle and syringe programs. Depot buprenorphine may play a key role in this regard.

Australia has clearly laid the foundations to meet the WHO elimination targets by 2030. Although COVID-19 has been a setback in many other areas of public health, we will get to the 'other side' hopefully in 2021, and can re-engage our efforts to strive for hepatitis C elimination. ⋖

Conflicts of interest: Gregory Dore is an advisory board member for and receives honoraria from Gilead, Merck and Abbvie. He has received research grant funding and travel sponsorship from Gilead, Merck and Abbvie.

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EDITORIAL

Naloxone for opioid toxicity and overdose in the community

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drug dependence, drug overdose, naloxone, opioids

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Opioid-related harms, especially accidental overdose deaths, have been increasing for over a decade. While there have been large increases in heroin deaths in the past five years,[1] approximately two-thirds of the more than 1000 opioid-related deaths per year are now from prescription opioids. Addressing inappropriate opioid prescribing is one way to reduce this death toll, however naloxone also has a role to play. Patients taking prescription opioids do not perceive themselves as being at risk of overdose, so there is a need for a broader conversation about opioid safety and toxicity. This conversation can involve the patient's family and friends. Naloxone is commonly associated with managing heroin overdoses but it should be considered for all opioid toxicity.

Naloxone acts as an opioid reversal drug by competitive antagonism at opioid receptors. It is safe to use and has no abuse liability. However, awareness of naloxone varies greatly by jurisdiction and patient population.[2,3] The Pharmaceutical Benefits Scheme (PBS) began subsidising naloxone in 2013. The drug was rescheduled in 2016 and is now available over-the-counter across Australia. However, when sold without a prescription there is no PBS subsidy, so naloxone can cost $50 or more. While both the rescheduling and the PBS subsidy were positive steps, unfortunately the actual amount of naloxone in the community has not increased as a result. Most naloxone was still being supplied as a PBS Prescriber Bag item rather than being obtained over-the-counter.[4]

In early 2019, the Australian Government therefore funded a pilot program in New South Wales, South Australia and Western Australia to provide naloxone free of charge through participating pharmacies and other services to people at risk of opioid overdose, and their carers and friends.[5] The pilot has been extended until June 2021. No data from this two-year pilot are available yet, but removing cost barriers could increase community access to naloxone. Importantly, naloxone should not only be considered for people who inject drugs. With the ever-increasing number of deaths involving prescription opioids, patients prescribed opioids for pain, particularly those on higher doses or with other risk factors for toxicity, could also benefit from improved community access to naloxone.

There are now two naloxone products available in Australia that are packaged to be suitable for administration by the public. The intramuscular formulation has been available for several years, but the skills needed to inject it can be a barrier to its use. In November 2019 an intranasal spray was listed on the PBS.[6] Administration is straightforward – a single metered dose is sprayed into one nostril. This formulation simplifies education on how to use naloxone and removes barriers for those who may not feel comfortable giving injections. A single intranasal dose (1.8 mg naloxone) is considered equivalent to the recommended initial intramuscular dose (0.4 mg) in the community setting. For either formulation, doses can be repeated every 2–3 minutes until there is a response or an ambulance arrives. If using the intranasal spray, repeated doses should be given into alternate nostrils.

Anyone who prescribes opioids for the treatment of pain or opioid dependence has an important role to play in discussing how to minimise harm. Ideally this discussion around opioid safety should include reviewing other drugs, especially central nervous system depressants, and a consideration of prescribing naloxone. Health professionals should be routinely and automatically discussing signs of opioid toxicity and the availability of naloxone with two main groups. These are firstly, all people receiving long-term opioids. Although those with opioid dependence who inject drugs are often knowledgeable about the signs to look out for, people prescribed opioids for pain generally have little knowledge about overdose.[3] Informing them can be both empowering and potentially lifesaving.[7] The second group that health professionals should be educating includes families, carers or significant others to identify the signs and symptoms of overdose. Having naloxone available can be reassuring for them when a patient is trying to reduce the use of prescribed opioids. They need to know when and how to administer naloxone and to always call an ambulance.

Health professionals should advocate for wide availability of naloxone in high-risk settings, such as community healthcare centres, homeless hostels and drug treatment programs including residential rehabilitation. Ensuring people have naloxone on hand in case of an emergency becomes even more important for anyone working in rural and regional areas. The longer wait times for an ambulance place even more emphasis on early intervention. Opioids

kill and injure through respiratory depression so every minute of anoxia counts.

Routine practice needs to change. Opioid-related deaths are increasing yet many are preventable. Proactive conversations about opioid safety should be part of routine care. Regularly discussing naloxone can help increase awareness of this lifesaving and safe medicine. Ensuring access can empower both the people at risk of harm and those who may witness and be able to respond to an overdose.

Conflicts of interest: Suzanne Nielsen has received unrelated research funding from Indivior and Seqirus (to study opioid dependence treatment and opioid-related harms). Suzanne Nielsen and Marianne Jauncey attended an advisory meeting on intranasal naloxone convened more than three years ago by Mundipharma (no fee was taken).

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LETTERS

Letters to the Editor

Caution with olanzapine use in dementia

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I found the article on limiting antipsychotic drugs in dementia excellent.[1] However, the antipsychotic deprescribing algorithm in Fig. 2 suggests considering a change to risperidone, olanzapine or aripiprazole.

I question why olanzapine has been suggested as an alternative. The reason for my concern is that treatment for behavioural and psychological symptoms of dementia (BPSD) occurs predominantly in older people (>65 years) with only a very small percentage being prescribed to younger patients.

Older people are very susceptible to adverse effects from drugs that exhibit clinically significant anticholinergic activity. This may include confusion, agitation, profound restlessness and hallucinations (similar to BPSD) and a worsening of dementia, as well as loss of visual acuity and dizziness, which increases the risk of falls.[2] Olanzapine exhibits clinically significant anticholinergic activity. It is also one of the most sedating antipsychotics, further increasing the risk of falls. (NPS MedicineWise has several resources covering medicines in dementia.)

In my role undertaking residential medication management reviews for people suffering from dementia in residential care, I am continually recommending that, where possible, olanzapine should be avoided in older people for the specific indication of treating BPSD, due to the high risk of anticholinergic adverse effects and sedation. I believe it is inappropriate to list olanzapine as an alternate antipsychotic to consider for the treatment of BPSD without also highlighting its high potential for anticholinergic side effects in the elderly (which may mimic BPSD), as well as its high risk of causing sedation.

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Stephen Macfarlane, one of the authors of the article, comments:

Mark Coles correctly highlights an important caveat in relation to the use of olanzapine in older people, particularly those with dementia.

The deprescribing algorithm which appeared in the article was reproduced with permission from Canadian Clinical Practice Guidelines.[1] While correctly suggesting the use of alternative antipsychotics in accordance with existing evidence-based guidelines, the algorithm is not without its flaws. The existing evidence base, by necessity, is limited by the studies that pharmaceutical companies have conducted for regulatory approval of their products for particular indications. There is evidence for both aripiprazole and olanzapine in the treatment of aggression in Alzheimer's disease.

Olanzapine certainly has significant anticholinergic properties which are dose dependent. A study found that olanzapine (5 or 10 mg) was significantly more effective than placebo in reducing agitation, aggression and hallucinations in a six-week study in 206 nursing home residents with Alzheimer's disease.[2] The 5 mg dose had the greatest effect, followed by the 10 mg dose, while 15 mg was no more effective than placebo. While it is possible that the lack of efficacy at the higher dose relates to the increasing anticholinergic load, the authors found that peripheral anticholinergic effects were significantly different from placebo in the 15 mg group only. However when central anticholinergic activity was measured, there were no differences found at any dose compared to placebo.

The correspondence reinforces the central tenets of our article that:

- no antipsychotic is a safe choice in this group
- numbers needed to treat are high
- antipsychotics often do more harm than good
- if antipsychotics are used, a deprescribing plan is needed to limit their duration.

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ARTICLE

Opioids and antidepressants: which combinations to avoid

SUMMARY

Some opioids such as tramadol, pethidine, dextromethorphan and tapentadol increase serotonergic activity. Fentanyl and methadone also do this but to a lesser extent.

These opioids may increase the risk of serotonin toxicity when combined with antidepressants.

Some selective serotonin reuptake inhibitors block the metabolism of opioids. This may reduce the concentrations and analgesic effect of some opioids such as codeine and tramadol, and increase the concentrations and risk of adverse effects of other opioids such as methadone.

Fluoxetine and irreversible monoamine oxidase inhibitors – tranylcypromine and phenelzine – have prolonged actions and may interact for weeks after they have been discontinued.

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Keywords
antidepressants, drug interactions, monoamine oxidase inhibitors, opioids, serotonin toxicity

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Introduction

Opioid dispensing increased fourfold in Australia from 1990 to 2014 and prescribing of antidepressants doubled from 2000 to 2016. The prescribing of both classes in combination is therefore increasingly common.[1,2] While many combinations have minimal risk, some may increase the risk of serotonergic effects and other toxicity, or reduce analgesic efficacy. The simplest preventive strategy is to generally avoid prescribing opioids associated with higher risks of interaction.

Opioids and serotonergic activity

The analgesic effect of opioids is mediated through three major opioid receptors – mu, delta and kappa. However, many opioids have actions on other targets, for example blocking serotonin and noradrenaline reuptake and N-methyl-aspartate (NMDA) receptors.[3] This is mostly a phenomenon with synthetic opioids. These additional actions may be beneficial or harmful and occur peripherally and in the central nervous system.[3]

Serotonin in the neuronal synapse is tightly regulated via multiple mechanisms – a key one involves the serotonin transporter. Some opioids inhibit the serotonin transporter which increases concentrations of serotonin in the synaptic cleft and therefore postsynaptic serotonin signalling.[4,5]

Toxicity

Serotonin toxicity or syndrome results from excessive serotonin and its severity depends on the amount of excess serotonin. The three main groups of features are:[6]

- neuromuscular hyperactivity – clonus, myoclonus, tremor, hyperreflexia, rigidity
- autonomic hyperactivity – fevers, tachycardia, diaphoresis, tachypnoea
- altered mental state.

Serotonin toxicity generally only occurs when serotonergic opioids are given with another serotonergic drug such as an antidepressant, even at therapeutic doses (see Box).[3] The highest risk opioid drugs are tramadol, pethidine and dextromethorphan.[7] The highest risk serotonergic drugs are the irreversible monoamine oxidase inhibitor (MAOI) antidepressants, tranylcypromine and phenelzine.[8] The risk and precautions with different combinations are summarised in the Table.[3,6,7,9] The highest risk for serotonin toxicity by far is with irreversible MAOIs and pethidine, tramadol or dextromethorphan.

There have been occasional case reports of serotonin toxicity with low-risk opioid and antidepressant combinations, such as oxycodone and buprenorphine/naloxone (Suboxone) with other serotonergic medicines.[10-13] Many of these reports have very obvious alternative medical explanations for all the signs of the alleged severe serotonin toxicity.[14] However, it also seems likely that moderate serotonin toxicity may occasionally be precipitated by any opioid in susceptible individuals taking an antidepressant, perhaps due to indirect effects of opioids on serotonin release. A high index of suspicion is therefore needed.[8] Similarly, antidepressants such as agomelatine, mianserin and reboxetine have a very low risk of serotonin syndrome but caution still might be warranted in combination with very high-risk serotonergic drugs.[3,5,7]

Box **Drugs likely to increase the risk of serotonin toxicity when combined with serotonergic opioids**[3]

Monoamine oxidase inhibitors

- irreversible inhibitors (phenelzine, tranylcypromine)
- reversible inhibitors of monoamine oxidase (moclobemide)
- non-antidepressant monoamine oxidase inhibitors (linezolid, methylene blue, lamotrigine)

Serotonin-releasing drugs

- appetite suppressants (fenfluramine, sibutramine)
- amphetamines (methamphetamine, methylphenidate, phentermine)
- synthetic stimulants (MDMA, cathinones)

Serotonin reuptake inhibitors

- selective serotonin reuptake inhibitors
- serotonin noradrenaline reuptake inhibitors
- tricyclic antidepressants (clomipramine, imipramine)
- serotonin modulators (vortioxetine)

Miscellaneous

- lithium
- St John's wort
- tryptophan
- buspirone
- triptans

MDMA 3,4-methylenedioxymethamphetamine

Table **The risk of serotonergic toxicity with combinations of antidepressants and opioids**[3,6,7,9]

	Antidepressants	
	Low–intermediate risk SSRIs, SNRIs, TCAs, St John's wort, lithium	**High risk** MAOIs (or previous history of serotonin toxicity)
Opioids		
Low risk Morphine, codeine,* buprenorphine, oxymorphone, hydromorphone, oxycodone	Should be safe	Possible rare interaction. Use with caution
Medium risk Fentanyl, tapentadol, methadone	Possible rare interaction. Use with caution	Increased risk of serotonin syndrome
High risk Tramadol,* pethidine, dextromethorphan	Increased risk of serotonin syndrome	Contraindicated

* risk of decreased analgesic effect
SSRI selective serotonin reuptake inhibitor
SNRI serotonin noradrenaline reuptake inhibitor
TCA tricyclic antidepressant
MAOI monoamine oxidase inhibitor

Inhibition of opioid metabolism

The two most commonly used 'weak opioids' codeine and tramadol require cytochrome P450 (CYP) 2D6 for conversion to an active opioid agonist. They consequently have less abuse potential which allows less restrictive scheduling in most countries. However, many antidepressants are CYP2D6 inhibitors (fluoxetine, paroxetine, and to a lesser extent duloxetine, fluvoxamine, sertraline, desvenlafaxine and escitalopram). This means combinations of codeine or tramadol with these antidepressants may lead to reduced analgesia.[15]

Conversely, inhibition of metabolism of other opioids (via a variety of enzymes) may lead to increased risks of opioid adverse effects. The combinations that are particularly of concern are specific to individual drugs such as tramadol, tapentadol, fentanyl and methadone.

Tramadol

While tramadol's main metabolite is an opioid agonist, it is remarkably similar in structure to venlafaxine, with similar inhibitory effects on noradrenaline and serotonin reuptake.[16,17] The combination of tramadol with an antidepressant is by far the most common serotonergic drug–drug interaction.[18,19]

As tramadol inhibits serotonin and noradrenaline reuptake, combinations with selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs) are likely to have additional adverse effects without added benefits. Inhibition of CYP2D6 by common antidepressants such as paroxetine and fluoxetine[20] not only reduces conversion of tramadol to an opioid agonist, it also results in higher concentrations of tramadol. Thus, these antidepressants both directly and indirectly increase the serotonergic and other adverse effects of tramadol, while potentially reducing analgesic efficacy.[16,21]

Seizures are a key adverse effect of tramadol and can occur in overdose.[22] Tramadol is also commonly implicated in new onset seizures with therapeutic use.[23] This risk is further heightened when it is co-administered with SSRIs, tricyclic antidepressants, venlafaxine and bupropion.[21,24-26]

Tapentadol

Tapentadol has different pharmacology to tramadol. It is an opioid agonist without active metabolites and a noradrenaline reuptake inhibitor with only weak effects on serotonin reuptake.[27] MAOI use is contraindicated with tapentadol and there have been many reports to regulatory agencies of serotonin toxicity with this combination.[7] MAOIs were also excluded from most tapentadol trials.[9] Currently, it is unclear if tapentadol has a greater risk of serotonin toxicity than other opioids.

Fentanyl

Fentanyl is a high-potency opioid agonist with no effect on serotonin reuptake and low affinity (relative to opioid receptor affinity) for postsynaptic serotonin receptors (5-HT_{1A} and 5-HT_{2A}).[5] Co-administration with an SSRI has been reported to cause an agitated delirium consistent with serotonin toxicity.[28] However, in a retrospective analysis of 4583 people who received fentanyl and another serotonergic drug, only 23 of them had adverse events and only four (0.09%) met the criteria for serotonin syndrome.[29] It is also unclear how fentanyl compares to other opioids in terms of the risk of serotonin syndrome. However, its combination with an MAOI is contraindicated.

Methadone

Methadone is largely used in the management of opioid dependence. It also has potential serotonergic effects with serotonin and noradrenaline reuptake inhibition and high affinity for serotonin receptors (5-HT_{2A} and 5-HT_{2C}).[5] Methadone has been associated with serotonin toxicity when given with other serotonergic medicines but the risk appears low.[7]

Methadone also has highly variable hepatic clearance via CYP3A4, CYP2B6 and CYP2D6. Most SSRIs and SNRIs inhibit one or more of these enzymes and might then precipitate methadone toxicity. Methadone and (es)citalopram both cause QT prolongation, thus providing yet another potential interaction.

Antidepressants and duration of risk

Avoiding high-risk combinations can be difficult and this is further complicated by three factors:

- many antidepressants have prolonged durations of action so patients may be at risk of interactions for two weeks after an irreversible MAOI is discontinued and five weeks after fluoxetine is discontinued[4,6,7]
- sudden cessation of short-acting antidepressants commonly causes withdrawal phenomena, which might even be misinterpreted as serotonin toxicity
- there are high rates of substance dependence and concomitant depression.

Other drug interactions

Sedating antidepressants such as tricyclics, tetracylics (mirtazepine and mianserin) and agomelatine in combination with opioids can exacerbate drowsiness which can increase the risk of falls and respiratory depression.[30]

Serotonergic drug interactions are not confined to antidepressants and opioids. For example, very severe interactions may occur with methylene blue and linezolid which inhibit monoamine oxidase and care should be taken when these are prescribed with opioids or antidepressants.

The combination of an opioid and drugs with anticholinergic effects can increase the risk of constipation, urinary retention and delirium.

Conclusion

Co-administration of antidepressants and opioids, deliberate or unplanned, is common. The risk of serotonin toxicity should be evaluated routinely but by far the highest risk is with MAOIs and pethidine, tramadol or dextromethorphan. Avoiding the routine use of any of these higher risk drugs is the simplest prescribing strategy. If there is an urgent need for opioids in someone taking an MAOI, using a non-synthetic opioid like morphine is preferred.

There are many kinetic interactions, adverse effects and withdrawal phenomena from all of these drugs. Clinicians should not assume that problems from combining these drugs can be explained by serotonin toxicity, and other obvious alternative medical explanations should also be considered. ≺

Conflicts of interest: none declared

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ARTICLE

Rational prescribing in community palliative care

SUMMARY

Palliative care is the province of everyone, particularly people managing older patients.

Most people die of multimorbidity, frailty and dementia rather than cancer and will never see a palliative care specialist.

People dying from non-malignant disease have symptoms and problems that are usually predictable. Common symptoms like pain and dyspnoea can be anticipated. Planning to prevent them, or for when they occur, is more effective than waiting until they happen.

Deprescribing is an effective way of preventing morbidity in this group.

Getting to know a few medicines well for each symptom is important when providing palliative care for patients. Starting at low doses and increasing slowly is also key.

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Keywords
deprescribing, end-of-life care, palliative care, primary care

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Introduction

By 2050, 25% of the Australian population will be over 65 years of age.[1] Between 2012 and 2061, the number of deaths per annum will rise by about 250%.[2] As the mortality of many previously fatal conditions has been reduced, a large proportion of deaths are due to dementia, multimorbidity, or frailty (or a combination of these).[3]

The way we think of managing dying has to change. At present, specialist palliative medicine covers deaths from cancer and very complex non-malignant conditions. In specialist palliative care services, 80% of the patients die of cancer[4] and yet only 20% of people over 70 die from cancer.[3] Hence, the burden of care of most dying patients falls elsewhere – in general practice, aged-care facilities and in general inpatient medicine.

Generally, people with life-limiting, non-malignant, multimorbid conditions die in predictable ways. However, the timeframe is very uncertain and can often take years. To better manage end-of-life care for these patients, planning is needed for when acute events happen, rather than reacting to events when they have already happened. This is termed anticipatory care or advance care planning.[5]

Advance care planning and deprescribing

Quality of life needs to be the primary goal of management for people who are near the end of life. Polypharmacy can impede quality of life through adverse drug effects and drug–drug interactions. Enacting a deprescribing strategy is an important first step (Box).[6] The physician needs to ask if each medicine maintains current wellbeing or prevents symptoms. In a frail older person there is little place for drugs like statins[7] which aim to prevent long-term cardiac or neurological events.

Medicines at the end of life

Much of palliative care management is non-pharmacological. Understanding and incorporating the patient's beliefs and wishes, along with good nursing care, are cornerstones of end-of-life care. Paying close attention to the carer's needs will also help facilitate a satisfactory conclusion to the patient's life.[8]

Evidence-based palliative care treatments, generally derived from people with cancer, are usually applicable to symptoms arising from non-malignant diseases.

Box **A deprescribing strategy in frail older people at risk of dying in the foreseeable future**[6]

1. Define care goals in the context of life expectancy, functional incapacity, quality of life, and patient and caregiver priorities
2. Ascertain all drugs taken
3. Identify patients at high risk of, or already experiencing, adverse drug reactions
4. Determine disease-specific benefit–harm thresholds that may support treatment discontinuation
5. Review the relative use of individual drugs
6. Identify drugs that may be discontinued or have their dosing modified
7. Implement and monitor a revised therapeutic plan with ongoing reappraisal of drug use and patient adherence

Adapted from reference 6

Australia's Pharmaceutical Benefits Scheme (PBS) has a palliative care section that lists treatments not on the general scheme. These medicines are often available in larger quantities than normal. Comprehensive information on the medicines available and their use is available in Therapeutic Guidelines, Palliative Care.[9]

Pain

Approximately 70% of cancer patients experience pain, as do many of those with non-malignant disease. Understanding the nature of the pain is critical in controlling it. Pain that arises from tissue damage (nociceptive pain) usually responds to simple analgesia and opioids. By contrast, pain from nerve compression, infiltration or destruction is often resistant to opioids.

Persistent pain requires regular analgesia. Paracetamol, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) should be considered initially, unless the pain is severe on presentation. NSAIDs should be used with caution in older people, particularly as renal impairment, cardiovascular disease, gastric symptoms and hypertension are common. If there are no absolute contraindications, short courses of NSAIDs can be used to reduce pain to a point where regular paracetamol will control it.

Opioid analgesia

While there is community concern about the use of opioid analgesia, it should not be withheld from people with ongoing, poorly controlled pain. Very low-dose opioids can provide excellent analgesia in frail older people with conditions like chronic osteoarthritic and spinal pain. Drugs such as buprenorphine patches and low-dose sustained-release oxycodone provide analgesia with low exposure to opioids. Co-existing conditions like renal impairment should be considered when dosing opioids, and vigilance to identify potential toxicity is essential.

There is a wide range of opioids available. It is sensible to be familiar with three or four and know their properties well. In particular, it is important to understand the relative potency of the drugs and their route of elimination. The lowest dose of fentanyl patches, for example, is the equivalent of a daily morphine dose of 40 mg. Using it in an opioid-naïve patient is likely to cause significant toxicity. However, fentanyl is entirely excreted by the liver, so is a good choice in severe renal impairment.

While tramadol and tapentadol bind to the mu opioid receptors, and thus are classed as opioids, they also work on noradrenaline and serotonin neurotransmitters, and so have widespread adverse effects including life-threatening serotonin syndrome.

Conversion tables and phone apps that allow rapid calculation of equivalent doses of different opioids are available. Examples include the evi-Q opioid dose calculator,[10] the Australian and New Zealand College of Anaesthetists Faculty of Pain Medicine's Opioid Calculator[11] and the GP Pain Help app.[12]

Adjuvant therapies

The amount of opioid analgesia required can be reduced by using drugs that reduce the intensity of the cause of the pain. For example, antispasmodics (e.g. hyoscine) can reduce the impact of an obstructed hollow viscus, like the gut or the ureter. Oral steroids and NSAIDs can reduce the oedema associated with a hollow viscus obstruction and are widely used in palliative care. Dexamethasone has less propensity to cause adverse effects than prednisolone, but long-term use leads to adverse effects. Infusions of bisphosphonates (e.g. pamidronate or zolendronic acid) can prevent pain from bony secondary tumours and lower the risk of fractures. They are also used to reverse hypercalcaemia.

Neuropathic pain

Neuropathic pain is frequently resistant to simple analgesics and opioids and requires adjuvants. One antiepileptic drug, pregabalin, is approved for neuropathic pain treatment. However, the dose range is enormous. Much of the neuropathic pain in older people will be managed with quite low doses. To minimise the risk of adverse effects, pregabalin should be started at the lowest possible dose of 25 mg twice a day, and slowly titrated upwards over several days. Antidepressants, particularly low-dose tricyclic antidepressants like amitriptyline, are very useful in this situation. Similarly, a slow titration (from a minimum of 10 mg daily to a maximum of 75 mg daily) is essential to minimise adverse effects.[9]

Dyspnoea

Dyspnoea, the sensation of breathlessness, may or may not be associated with hypoxia. Chronic and acute severe dyspnoea are very distressing. Simple measures like sitting the patient up, and directing a fan onto their face or opening windows improve dyspnoea. Breathing techniques as taught by physiotherapists, and psychological therapies can be very useful. Oxygen can be used in hypoxic dyspnoea, but is no better than air in treating the sensation of chronic dyspnoea.[13]

Sometimes drugs are necessary. Opioids have strong evidence of reducing chronic dyspnoea,[14,15] and do not cause respiratory depression if introduced at low doses. Morphine sulfate pentahydrate (Kapanol), a long-acting preparation, has recently been listed on the PBS for chronic dyspnoea.

Acute episodes can be settled rapidly with sublingual lorazepam 0.5–1 mg. This is one situation where a low dose of continuous benzodiazepines may be warranted.

Nausea and vomiting

Nausea and vomiting should be addressed promptly. A number of treatments are available in the community, notably metoclopramide and oral haloperidol. While evaluating the cause of the nausea and treating it directly is important, haloperidol 1.5 mg over 24 hours is effective regardless of the cause.[16] Methotrimeprazine is effective[17] but is only available through the Special Access Scheme. However, some public hospital services will have it.

Constipation

Constipation is ubiquitous in frail older people due to limited diet, reduced peristalsis, weakened musculature and the frequent use of opioids and anticholinergic drugs.[18] Avoid fibre supplements as reduced peristalsis rather than lack of fibre is the principal cause. Stimulant laxatives (e.g. senna, bisacodyl) enhance peristalsis. The osmotic laxative macrogol is effective and widely used.

Confusion and delirium

Non-drug approaches such as low lighting, familiar surroundings and people (in small numbers) are very effective in reducing the impact of confusion and delirium. Once treatable causes have been excluded, oral or subcutaneous benzodiazepines such as clonazepam (oral or subcutaneous) or midazolam (subcutaneous) can be used to reduce the anxiety. Atypical antipsychotics and haloperidol worsen the symptoms of delirium compared with placebo and have additional adverse effects.[19]

Fatigue, anorexia and weight loss

Fatigue, anorexia and weight loss are very common in dying patients, particularly those with dementia or advanced cancer. Patients and their carers need to understand that these are inevitable consequences of advanced cancer and are not because of starvation. More food, or nutritional supplements, do not reverse the problem. Some medicines can be tried if these symptoms are causing significant distress. However, multiple medicines have been tried with partial success at best. Steroids can improve appetite but are associated with a large dropout rate due to adverse effects like hyperglycaemia and gastrointestinal bleeding.[20] Progestogens can increase appetite and weight but carry an increased risk of oedema and thrombotic events.[21] About a quarter of people with end-stage cancer-related fatigue will experience improvement with methylphenidate.[22]

Conclusion

Most end-of-life care in the community will be delivered by primary care and other non-specialist medical services. Anticipating likely complications and planning for them is the key to high-quality palliative care. Medicines can be very useful in minimising symptoms, but should be used at low doses with regular patient monitoring. Anticipation of symptomatic needs, and early decisive treatment can minimise the impact of symptoms in older people suffering non-malignant disease at the end of their life. <

Conflicts of interest: none declared

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ARTICLE

Balancing the benefits and harms of oral anticoagulation in non-valvular atrial fibrillation

SUMMARY

Non-valvular atrial fibrillation is becoming more common in Australia and globally.

The direct oral anticoagulants apixaban, dabigatran and rivaroxaban offer an improved safety profile over warfarin.

Patient preferences are important and shared decision-making supports better adherence to treatment.

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Keywords
anticoagulants, apixaban, atrial fibrillation, dabigatran, haemorrhage, rivaroxaban, thromboembolism

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Introduction

The decision to start, continue or stop oral anticoagulation is common and challenging in patients with non-valvular atrial fibrillation. A disabling stroke is a disaster for the patient and their family, as is a disabling or fatal bleed.

Increasing prevalence of atrial fibrillation

The most common reason to prescribe anticoagulation is for thromboembolic prophylaxis in clinically diagnosed atrial fibrillation or paroxysmal atrial fibrillation. Unlike some risk factors for stroke (blood pressure, cholesterol, smoking), the prevalence and incidence of atrial fibrillation is increasing globally. This is possibly due to increasing obesity and an ageing population, including more people surviving with chronic heart disease.[1]

In Australia, stroke physicians see many patients with large artery occlusion due to embolic stroke (perhaps up to 40% of ischaemic stroke). The majority of these patients are in atrial fibrillation but are not anticoagulated, emphasising the gap between evidence and practice.[2,3]

Patient preferences

To understand the factors that influence treatment success, it is important to know patient preferences. A recent systematic review[4] found that patient preferences do not align well with anticoagulation guidelines, with perhaps only two-thirds of patients accepting guideline-recommended treatment. Patients are willing to accept the risks of bleeding to prevent stroke if this represents an absolute risk reduction of at least 1% per year. The review also found that physicians put more weight on bleeding risks, and patients put more weight on stroke reduction. Convenience was also an important factor for patients – including once a day treatment, no bridging requirement (intravenous heparin or subcutaneous low-molecular-weight heparins), no food interactions and no need for monitoring.[4] If these patient and physician preferences are considered, the direct oral anticoagulants (DOACs) such as apixaban, rivaroxaban and dabigatran can be seen as a useful advance. Shared decision-making is key and ensures that patients and their families are clear partners in the conversation.[5]

Direct oral anticoagulants versus warfarin

Trial evidence showing that DOACs were non-inferior (or superior) to warfarin for prevention of ischaemic stroke has been matched in routine clinical practice.[6] They may also be associated with less discontinuation by patients (in the USA) compared to warfarin. However, discontinuation remains common with DOACs and warfarin, and this issue needs to be part of shared decision-making.[5,7,8]

A comparative meta-analysis found that DOACs have a lower risk of intracranial haemorrhage and a higher risk of gastrointestinal bleeding than warfarin.[9] Given the changing evidence together with patient preferences, it is no surprise that since 2014 more people needing oral anticoagulation have been started on DOACs rather than warfarin in Australia.[10]

Australian practice

There is evidence of under- and over-treatment of those in atrial fibrillation – in many cases this is due to clinicians not following guidelines.[11] These recommend that the decision to anticoagulate should be based on the sexless CHA_2DS_2-VA score

(see Table).[12] Approximately 75% of patients for whom oral anticoagulation is recommended (CHA_2DS_2-VA score ≥2) do not receive it and about a quarter of those who should not receive it (score of 0) do receive it.[11] Given this large discrepancy between the evidence and clinical practice, it is important to review the current national guidelines.[12,13]

When oral anticoagulation is recommended, further assessment of the patient is required. This needs to take account of the patient's preferences and expectations,[5] the presence of contraindications and whether any of these are modifiable. For example, if a patient has troublesome haemorrhoids that bleed, treating them (e.g. by injection or surgery) could allow safer oral anticoagulation in the future. Other potentially modifiable factors include falls, alcohol intake, uncontrolled hypertension and other medicines such as non-steroidal anti-inflammatory drugs and antiplatelet drugs.

Bleeding risk

When weighing up the risks and benefits of anticoagulation, it is useful to consider the following:

- the main types of serious bleeding – intracranial and gastrointestinal
- important patient factors – renal failure, older age, concomitant antiplatelet therapy.

Risk scores have been developed to predict bleeding in patients on anticoagulants. Unfortunately, these have not been as clinically useful as hoped because the likelihood of stroke and the likelihood of bleeding both increase with risk factors such as age. However, the individual components of the score (such as uncontrolled hypertension, excessive alcohol intake or concomitant antiplatelet drugs) can be targeted for intervention to reduce potential risks.

Intracranial bleeding

The most severe bleeding complication is intracranial bleeding. In a systematic review of pivotal trials, DOACs were associated with a halving of intracranial haemorrhage compared with vitamin K antagonists.[9] A similar reduction was noted in subsequent observational studies.[14]

If patients have an intracranial bleed on oral anticoagulants, emergency reversal is associated with better outcomes. Patients should be advised to go to hospital immediately if they develop stroke-like symptoms. Reversal regimens are most readily available for those on warfarin and dabigatran.

Gastrointestinal bleeding

Gastrointestinal bleeding occurs twice as commonly as intracranial haemorrhage but has a lower mortality and lower long-term morbidity. DOACs are associated with a 25% increase in gastrointestinal bleeding events compared to vitamin K antagonists. Again, similar patterns were noted in the observational studies (although this might not be the case for all DOACs).[6,9]

Renal impairment

Oral anticoagulation for those in renal failure is complicated by two main factors. The DOACs are renally excreted and therefore need renal dose adjustment and are not recommended in severe renal failure. Dabigatran is recommended for use only when creatinine clearance is over 30 mL/minute. Rivaroxaban has recently been approved for use when creatinine clearance is over 15 mL/minute, with caution, using the 15 mg daily dose. Apixaban should only be used when creatinine clearance is over 25 mL/minute. Warfarin is the only choice of oral anticoagulant for those with creatinine clearance less than 15 mL/minute or on dialysis. However, there are no reliable randomised controlled trial data that show warfarin is beneficial for stroke prevention in these patients (as renal failure is associated with an increased risk of bleeding).[12]

Age and blood pressure

Older people have a greater risk of stroke in atrial fibrillation (see CHA_2DS_2-VA score in the Table) and therefore still benefit from treatment despite the increased risk of bleeding. The Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) found that warfarin was superior to aspirin for

Table **Definition and scoring of CHA_2DS_2-VA to guide oral anticoagulant therapy in non-valvular atrial fibrillation**

Item	Definition	Points
C	Heart failure	1
H	Hypertension	1
A_2	Age ≥75 years old	2
D	Diabetes	1
S_2	History of stroke/transient ischaemic attack/systemic embolus	2
V	Vascular disease (myocardial infarction, peripheral vascular disease or known complex atheroma)	1
A	Age 65–74 years	1

Recommendations

Score = 0: oral anticoagulant or antiplatelet drugs not recommended

Score = 1: consider oral anticoagulants

Score ≥2: oral anticoagulants recommended

Recommendations adapted from the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand Clinical Guidelines[12]

stroke prevention in people aged 75 years and over (average age 81.5 years), with an annual absolute stroke prevention rate of 2%. The extracranial bleed rate was similar in the warfarin and aspirin groups.[15] This trial is particularly important as it demonstrated that, with good blood pressure control (85% with a blood pressure below 160 mmHg systolic), rates of intracranial haemorrhage were low (<1% a year). The Australian national guidelines also mention the importance of blood pressure control as a method of reducing bleeding.[12]

Falls

Fall assessment is particularly important as falls are a common cause of death in older Australians – the death rate from falls is about a third of the death rate from stroke.[16] The risk of dying following a fall is greatly increased for those on oral anticoagulation due to the increased risk of intracranial haemorrhage. This is mainly from subdural haemorrhage, but also includes subarachnoid haemorrhage and intracerebral haemorrhage.[17-19] There are no reliable mortality data to know the size of this risk in Australia but data elsewhere suggest this could be in the hundreds per year.[16-19]

A holistic assessment such as a comprehensive geriatric review may help to weigh up the risks and benefits of oral anticoagulation for those at a high risk of falls. It is good practice to ask about any falls before starting anticoagulation, and at all subsequent reviews. Apixaban has been shown to be substantially better than aspirin for those with contraindications to warfarin,[20] with additional benefits including dose adjustment by age, weight and renal function.

Antiplatelet drugs

Finally, clinicians need to be aware that combining oral anticoagulation with antiplatelet drugs always increases the risk of bleeding. However, the reduced risk of thrombotic events may justify this risk for short periods (e.g. after cardiac stenting).[12] Clinicians need to ensure that an appropriate step down to a double or single antithrombotic regimen is carried out in a timely manner, depending on the circumstances.[12]

Conclusion

The introduction of the DOACs has been an advance in medicine, with their improved safety profile. However, there is evidence of considerable over- and under-treatment with oral anticoagulants in Australia. Strategies to improve compliance with guidelines need to be considered to improve health outcomes. ◀

Conflicts of interest: none declared

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ARTICLE

Discontinuation of antiepileptic drugs in adults with epilepsy

SUMMARY

Patients with epilepsy who have been free of seizures for at least two years may be able to stop their antiepileptic drugs. Discontinuation may be considered after an individualised harm–benefit assessment and consultation with a neurologist is recommended.

It is paramount to discuss with patients whether the risk of seizure recurrence is worth the benefit of stopping the antiepileptic drug.

The risk of seizure recurrence after antiepileptic drugs are discontinued depends on the epilepsy syndrome and a number of other risk factors. Approximately 30–50% of patients will relapse.

If seizures recur, the majority of patients regain seizure control when treatment is resumed. However up to 20% do not achieve immediate remission.

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Introduction

Antiepileptic drugs are effective in stopping seizures in approximately two-thirds of patients with newly diagnosed epilepsy.[1] However, it is impossible to know in patients who are seizure-free for a long time whether the absence of seizures is due to seizure suppression by their treatment, or due to remission of the epilepsy.

A decision to continue or to stop antiepileptic drug treatment requires an individualised harm–benefit assessment. The main concern is the recurrence of seizures after treatment stops. A number of factors need to be considered when assessing the risk of recurrence. It is important to include patients in the discussion of whether this risk is worth the benefit of stopping treatment.

Reasons to consider discontinuation

Up to 88% of patients experience adverse effects from antiepileptic drugs. These include dizziness, sedation, cognitive and neuropsychiatric symptoms, which can negatively affect quality of life.[2] There are also concerns regarding bone health and an increased risk of fractures as a long-term complication with some antiepileptic drugs.[3]

Women of childbearing age often worry about the potential teratogenicity of antiepileptic drugs. This may be a motivation to attempt to reduce their antiepileptic drugs, ideally long before actually planning a pregnancy. While it is important to limit exposure to teratogenic antiepileptic drugs during pregnancy, abrupt cessation should be avoided. Some antiepileptic drugs have a known (often dose-dependent) risk of teratogenicity. Valproate has the highest risk of major congenital malformations. Other drugs are considered safer with lamotrigine and levetiracetam having the lowest risk.[4] For many newer antiepileptic drugs the risk of harm is still unknown.

Antiepileptic drugs, such as carbamazepine and phenytoin, affect important hepatic enzyme systems such as cytochrome P450. They can have significant pharmacological interactions such as reducing the efficacy of oral contraceptive pills, oral anticoagulants (warfarin and direct oral anticoagulants) and direct-acting antiviral drugs for chronic hepatitis C. Patients with chronic hepatitis C are usually required to either taper their therapy or switch to an alternative antiepileptic drug before starting antiviral treatment.

Other reasons for discontinuation may include the cost of treatment. There is also the wish to feel 'cured' and to avoid the inconvenience and stigma of taking drugs daily.

The discussion about antiepileptic drug discontinuation should prompt review of the original diagnosis and supporting evidence. Patients with an equivocal history of seizures or patients who never fulfilled the diagnostic criteria for epilepsy (e.g. acute symptomatic seizures or prophylactic use of an antiepileptic drug) should be evaluated again to see if there is any indication for continuing treatment.

It is important to explore the patient's concerns and motivation for antiepileptic drug withdrawal. There may be alternatives for the patient to consider such as dose reduction or change of antiepileptic drug to address adverse effects, pharmacological interactions or teratogenicity. Some patients may only need clarification and reassurance regarding the safety profile of their antiepileptic drug.

Risk of seizure recurrence

The main risk associated with discontinuing antiepileptic drug therapy is seizure recurrence. This occurs in 26–63% of cases depending on the patient population.[5-7] A meta-analysis of 10 studies including 1769 patients with varying characteristics found a seizure recurrence rate of 46% after antiepileptic drugs were stopped.[5] The rate of seizure recurrence within the same time period is about twice the rate reported with continued treatment.[6,8] The risk is highest within the first 6–12 months after discontinuation, but remains substantially increased for many years.[5,6]

Seizure recurrence can have devastating physical, psychological and social consequences. These may include injury, loss of self-esteem, stigma around seizures, unemployment and the inability to drive.

Some patients are willing to stop antiepileptic drugs even when the risk of relapse is substantial, whereas others fear the return of seizures and decide to continue their antiepileptic drugs. In one study, more than half of the patients preferred to continue their antiepileptic drug after two years of seizure freedom. They felt well-adjusted to their treatment and were concerned about possible seizure recurrence after withdrawal and the subsequent loss of their driving licence or even their jobs.[9]

Factors associated with seizure recurrence

A large meta-analysis identified independent predictors of seizure recurrence after treatment stops (see Boxes 1 and 2).[5] The authors of the analysis created an easy-to-use web-based epilepsy prediction tool to assist clinicians when counselling patients. This tool is particularly useful in patients with some predictors in favour and others against stopping treatment. It calculates an individualised risk of seizures in the next two and five years after antiepileptic drug withdrawal, and the chance to be seizure-free after 10 years. The calculator should not be used as a substitute for an individualised discussion of the full range of harms and benefits, but it helps substantially to guide tailored choices by the doctor and patient.

The type of epilepsy should always be included in the decision-making process before treatment is discontinued. The risk of seizure recurrence even after many years of being seizure-free is particularly high for patients with juvenile myoclonic epilepsy or focal epilepsy with a structural aetiology, which are the most common epilepsies in adults.[5,8,10]

Important considerations for counselling

Patients need to understand the potential problems that can occur after stopping treatment, particularly the consequences of relapse.

Regaining seizure control after relapse

If patients have seizures after stopping treatment, they have a good chance of becoming seizure-free again by resuming their drugs. However, up to 20% of patients do not achieve immediate remission and, for some patients, it may take several years to become seizure-free again.[11]

Driving

The implications for driving when discontinuing treatment are important to discuss with the patient. This may be the sole reason a patient decides against stopping antiepileptic drugs.

In Australia patients must stop driving while being weaned off antiepileptic drugs and for an additional three months after the last dose, in accordance with the Assessing Fitness to Drive Framework (private vehicle driver standard).[12] It is reasonable to extend this period in patients with a previously low seizure frequency to confirm that their freedom from seizures is sustained. If there is seizure recurrence, patients may resume driving if the previously effective treatment is resumed and there have been no seizures for four weeks.

Box 1 **Factors associated with an increased risk of seizure recurrence**[5]

Long duration of epilepsy before remission
Short seizure-free interval before antiepileptic drug withdrawal
Older age at onset of epilepsy (in patients >25 years)
History of febrile seizures
More than 10 seizures before remission
Absence of a self-limiting epilepsy syndrome e.g. absence or rolandic epilepsy
Developmental delay
Epileptiform abnormality on EEG before withdrawal

Box 2 **Factors associated with long-term seizure freedom (at 10 years after antiepileptic drug withdrawal)**[5]

Short duration of epilepsy before remission
Long seizure-free interval (years) before antiepileptic drug withdrawal
One or low number of antiepileptic drugs before withdrawal
Low number of seizures before remission
No history of focal seizures
No epileptiform abnormality on EEG before withdrawal

Drugs with other indications

Several antiepileptic drugs have additional beneficial effects, for example mood stabilisation in bipolar disorder (valproate, carbamazepine and lamotrigine) and migraine prophylaxis (topiramate, valproate). Monitoring for recurrence of these symptoms after the antiepileptic drug is withdrawn is recommended for patients who have these comorbidities.

Psychosocial impact

The antiepileptic drug weaning period may be associated with significant anxiety. This can be regarding seizure recurrence, restricted social activities and a possible impact on employment and driving.

Drug withdrawal after surgery for epilepsy

Resective epilepsy surgery aims to remove the epileptogenic zone and offers the chance of a cure. The risk of seizure recurrence after discontinuing antiepileptic drugs is one in three for patients who are seizure-free following surgery.[13] There are no guidelines for postoperative antiepileptic drug withdrawal in seizure-free patients. Practices vary widely across specialist centres, however, one year is a common time frame. The decision if and when to stop antiepileptic drugs must be individualised. It depends on the type of epilepsy surgery, aetiology of the epilepsy, the completeness of the resection and the patient's attitude to discontinuation. This is usually discussed as part of the postoperative care at the epilepsy centre.

When to stop antiepileptic drugs

Drug discontinuation may be considered after a minimum of two years without a seizure. The risk of recurrence decreases with every additional year of seizure freedom.[5,10] However, the two-year threshold is an artificial construct and should now be replaced by an individualised approach and a thorough examination of all the risks and benefits for each patient.[5]

In patients with an increased risk of seizure recurrence, it is advisable to wait longer than two years before considering antiepileptic drug discontinuation. The same is true for patients who had a low frequency of seizures (e.g. less than once a year) before remission.

Patients with a significant risk of seizure recurrence should not be encouraged or even advised to discontinue antiepileptic drugs even after a long period of seizure freedom. They include patients with juvenile myoclonic epilepsy, who only have a small chance of successful antiepileptic drug withdrawal.[14]

How to stop antiepileptic drugs

Most guidelines encourage slow discontinuation of antiepileptic drugs. However, the duration of the tapering period varies greatly and depends on multiple factors such as the number of antiepileptic drugs, the starting dose, previous seizure frequency, seizure type and associated risk of injury, risk of withdrawal seizures with some antiepileptic drugs and the non-driving period. Patients on multiple antiepileptic drugs need to withdraw them sequentially. The tapering schedule should ideally be provided by a neurologist after taking all relevant factors into account and discussing them with the patient. The taper duration will also be influenced by the patient's needs and preferences.[10] A slow taper (e.g. over months) allows observation and helps to document the minimally effective doses in case the seizures recur. However, a slow taper prolongs the non-driving period.

The taper rate for benzodiazepines (especially clonazepam) and barbiturates should be particularly slow. This reduces the risk of withdrawal symptoms and withdrawal seizures.

Management of seizure recurrence

If seizures recur, the previously effective drug should be restarted unless it was discontinued because of unacceptable side effects, in which case an alternative could be tried. Similarly, a woman of childbearing age whose seizures recur after stopping a teratogenic antiepileptic drug could be started on a drug with a lower teratogenic risk.

Conclusion

The decision to continue or to stop antiepileptic drugs in seizure-free adults requires an individualised harm–benefit assessment. The risk of seizure recurrence depends on a number of factors and there are tools available to assess this in individual patients. Social aspects such as driving and employment, as well as emotional and personal factors, must be carefully considered along with adverse effects and drug interactions. The doctor's role is to provide detailed information to help the patient make an informed decision. <

Conflicts of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

1. Patients with juvenile myoclonic epilepsy can successfully stop antiepileptic drugs when they reach adulthood.
2. When discontinuing treatment for patients taking multiple antiepileptic drugs, the drugs should be withdrawn sequentially.

Answers on page 71

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New drugs

BNT162b2 COVID-19 vaccine

Approved indication: prevention of COVID-19

Comirnaty (Pfizer)
multidose vials containing 0.45 mL suspension for dilution

In March 2020, the World Health Organization declared that the COVID-19 outbreak was a pandemic. Since then, there have been over 111 million confirmed cases worldwide and over 2.4 million deaths resulting from SARS-CoV-2 viral infection (WHO COVID-19 dashboard).[1] In response, hundreds of vaccines are being rapidly developed in an effort to prevent further disease.[2]

The BNT162b2 COVID-19 vaccine was the first to be given provisional approval in Australia and is indicated for those aged 16 years and over. It is made up of single-stranded messenger RNA (mRNA) which encodes the viral spike protein of the SARS-CoV-2 virus. The RNA is encapsulated in lipid nanoparticles which allows uptake by antigen-presenting cells (e.g. dendritic cells). Once inside, the mRNA is translated into the spike protein by host-cell machinery and presented on the cell surface. These antigen-presenting cells then show the spike protein to other immune cells including B cells which produce anti-spike protein antibodies.

The approval of this vaccine is based on short-term efficacy and safety data from an ongoing global trial. In the phase I part of the study, basic safety data including reactogenicity and immunogenicity of the vaccine were established.[3] Two 30 microgram doses given intramuscularly 21 days apart were found to elicit high titres of neutralising antibodies to the SARS-CoV-2 virus and robust cell-mediated responses involving CD8 and CD4 T cells.[4] This dosing regimen was progressed into the phase II/III part of the trial,[5] which randomised 43,548 participants (aged 16–91 years) 1:1 to receive the vaccine or a matching placebo.

The primary outcome of the phase II/III study was efficacy against COVID-19 disease onset at least seven days after the second dose in participants who were naïve to the SARS-CoV-2 virus. During the surveillance period, there were eight cases of COVID-19 among those who received the vaccine and 162 cases among those who received placebo. This equates to a vaccine efficacy of 95% (confidence interval (CI) 90.3–97.6%). A subgroup analysis found that protective efficacy was similar regardless of age, sex, ethnicity, obesity and co-existing hypertension.[5]

There were also less COVID-19 cases with the vaccine compared to placebo after the first dose but before the second dose (39 vs 82 cases) indicating that one dose of the vaccine confers some protective efficacy (52%, CI 29.5–68.4%). Severe COVID-19 occurred in one person who received the vaccine after the first dose and nine people who received placebo.[5]

In a safety cohort of 21,744 people who received at least one vaccine dose, the most common adverse events were injection-site pain (>80% of patients), fatigue (>60%), headache (>50%), myalgia and chills (>30%), arthralgia (>20%) and fever and injection-site swelling (>10%). Most reactions were mild to moderate in severity and often occurred at a higher frequency after the second vaccine dose. In general, older participants reported fewer and less severe adverse events. There were four cases of Bell's palsy with the vaccine versus none with the placebo. In the phase II/III part of the study, there were two deaths in the vaccine group (from arteriosclerosis and cardiac arrest) and four in the placebo group (deemed not related to study intervention).

Anaphylaxis has been reported with this vaccine following its rollout in the UK and USA. Two cases in the UK were in people who had a history of severe allergic reactions. Close observation for at least 15 minutes after vaccine administration is recommended and the second dose should not be given to someone who had an anaphylactic reaction with the first dose. Vaccination is appropriate in those with minor infections or low-grade fevers but should be postponed in those with acute severe febrile illness.

There have so far been no interaction studies with the vaccine. It is unclear whether it can be given at the same time as other vaccines.

There are limited data on use of the vaccine during pregnancy and lactation. Studies in animals did not indicate any harmful effects. Given the low level of community transmission in Australia, routine use of COVID-19 vaccines during pregnancy is not currently recommended by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists.[6] However, its guidance states that vaccination may be considered in some groups with a high risk of complications from COVID-19. Pregnant healthcare workers in an at-risk work environment should be

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Related articles:
ChAdOx1-S vaccine for prevention of COVID-19
COVID-19 vaccines – are we there yet?

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.

NEW DRUGS

allocated to lower-risk duties, work from home or take leave of absence. If this is not possible, they should be offered vaccination. The Australian Department of Health has published a guide to help women making decisions about vaccination during pregnancy and breastfeeding.

The vaccine is supplied in frozen multidose vials. Once thawed, the vaccine should be diluted with 1.8 mL of normal saline. This allows for administration of six 0.3 mL doses using low dead-volume syringes and needles. Opened vials should be discarded after six hours. Training modules for vaccination providers have been developed by the Department of Health in partnership with the Australian College of Nursing to ensure COVID-19 vaccines are administered safely.

The vaccine should be given by intramuscular injection into the deltoid muscle of the upper arm. The patient's name and the batch number of the vaccine must be recorded in the Australian Immunisation Register. Enhanced monitoring of adverse events following COVID-19 vaccination is in place at national and state and territory levels.[2]

This vaccine appears to be well tolerated and very effective at preventing COVID-19. Duration of protection is not currently known, and clinical trials are ongoing. Although the Australian Government's COVID-19 vaccination plan is for vaccines to be universally available, free and voluntary, they will initially be rolled out to priority groups including quarantine and border workers, frontline health workers, and staff and residents in aged care. Other vulnerable groups and high-risk workers will be targeted in later phases before the vaccine is rolled out to everyone.

T manufacturer provided the AusPAR and the product information

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

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

ChAdOx1-S vaccine

Approved indication: prevention of COVID-19

COVID-19 Vaccine AstraZeneca multidose vials containing 5 x 10^{11} viral particles in 5 mL

In March 2020, the World Health Organization declared that the COVID-19 outbreak was a pandemic. Since then, there have been over 114 million confirmed cases worldwide and over 2.5 million deaths resulting from SARS-CoV-2 viral infection (WHO coronavirus disease dashboard).[1] In response, many vaccines are being rapidly developed in an effort to prevent further disease.[2]

ChAdOx1-S (also known as the Oxford/AstraZeneca vaccine) is the second COVID-19 vaccine to be given provisional approval for use in Australia following the BNT162b2 Pfizer vaccine. ChAdOx1-S is a viral-vectored DNA vaccine that consists of a replication-deficient adenovirus which carries the gene encoding the SARS-CoV-2 spike protein. Following injection, the viral vector is taken up by immune cells, such as dendritic cells, and the gene is translated into the spike protein. These antigen-presenting cells show the spike protein to other immune cells, including B and T cells. This triggers the production of antibodies to the spike protein.

The provisional approval of this vaccine is based on short-term efficacy and safety data from four ongoing randomised controlled trials involving 23,848 people.[3] A phase I trial established early safety and immunogenicity of the vaccine (COV001 conducted in the UK)[4] and also included an efficacy cohort. Phase II and III trials (COV002 in the UK,[5] COV003 in Brazil and COV005 in South Africa) had an expanded enrolment to include a wider population that were more likely to be exposed to the SARS-CoV-2 virus (e.g. health workers).

Initial studies found that the vaccine elicited neutralising antibodies and cell-mediated responses to SARS-CoV-2.[4-6] Its efficacy is based on an interim analysis of the phase II/III studies (COV002, COV003).[3] Most of the 11,636 participants included in the interim analysis were 18–64 years old. Although the studies excluded people with severe comorbid illness or severe immunosuppression, mild comorbidity (e.g. obesity (BMI ≥30 kg/m^2), heart disease, respiratory conditions or diabetes) was permitted and accounted for 36% of those in the efficacy analysis.

Participants were randomised to the ChAdOx1-S vaccine or a control (meningococcal group A, C, W and Y conjugate vaccine), given by intramuscular injection. Those in the COVID-19 vaccine group received either two standard doses (5 x 10^{10} viral particles/injection) or a low dose (2.2 x 10^{10} viral particles/injection) followed by a standard dose. Because of logistical problems, the interval between doses varied from 4 to 26 weeks.

The primary efficacy outcome was protection against COVID-19 disease at least two weeks after the second dose in participants who had no previous evidence of SARS-CoV-2 infection. During the surveillance period, there were 30 cases of COVID-19 among those who received the vaccine and 101 cases among those who received the control. This equated to a vaccine efficacy of 70.4%. Vaccine efficacy was 59.3% in those who received two standard doses (the licensed vaccine regimen in Australia) and 90% in those who received a lower first dose followed by a standard second dose (see Table).[3]

In a subgroup analysis of those given two standard doses, vaccine efficacy tended to be higher when the duration between doses was longer (53.3% at <6 weeks, 51.1% at 6–8 weeks, 61% at 9–11 weeks and 79% at ≥12 weeks). The vaccine appeared to reduce

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Related articles:
BNT162b2 COVID-19 vaccine for prevention of COVID-19
COVID-19 vaccines – are we there yet?

Table **Efficacy of the ChAdOx1-S vaccine against COVID-19 disease**[3]

COVID-19 vaccine dosing regimen*	Cases of COVID-19		Vaccine efficacy†
	ChAdOx1-S vaccine	Meningococcal vaccine	
Low dose followed by a standard dose, or two standard doses	30/5807	101/5829	70.4% (CI 54.8–80.6)
Low dose followed by a standard dose	3/1367	30/1374	90% (CI 67–97)
Two standard doses	14/1879	35/1922	59.3% (CI 25.1–77.9)

CI confidence interval

* Low doses contained 2.2 x 10^{10} viral particles/injection and high doses contained 5 x 10^{10} viral particles/injection. Doses were given 4–26 weeks apart.

† Defined as protection against COVID-19 disease at least two weeks after the second dose in participants who had no previous evidence of SARS-CoV-2 infection

NEW DRUGS

COVID-19 hospitalisations compared to the control vaccine (0/6307 vs 9/6297 cases), measured 22 days after receiving a standard first dose.

Having one or more mild comorbidities at baseline did not appear to affect the protective efficacy of the vaccine (73.4%). Although the vaccine was immunogenic in people aged 65 years and older, vaccine efficacy could not be established as there were not enough cases of COVID-19 in this age group.

In a safety cohort of 12,021 vaccinated people, the most common adverse events were injection-site tenderness (>60%) and injection-site pain (>50%), fatigue and headache (>50%), myalgia and malaise (>40%), fever and chills (>30%), and arthralgia and nausea (>20%). Most reactions were mild to moderate in severity and resolved within a few days. Paracetamol appeared to reduce these reactions.[4] Adverse events were milder and less commonly reported after the second dose compared to the first dose. Older participants (≥65 years) reported fewer and less severe adverse events.

There were two serious adverse events in the vaccine group – one case of multiple sclerosis and one case of transverse myelitis. Both were thought unlikely to be related to vaccination. There were also two deaths in the vaccine group and four deaths in the control group. None were thought to be related to the vaccines received in the trial.

Vaccination should be postponed in those with acute severe febrile illness. Anaphylaxis can occur with any vaccine so emergency medical treatment and supervision should be available to manage anaphylactic reactions and observation for 15 minutes after vaccination is prudent. Caution is urged in people with thrombocytopenia, a bleeding disorder, or who are receiving anticoagulation therapy.

As with the BNT162b2 Pfizer vaccine, there are limited data on the use of this vaccine during pregnancy and lactation. Given the low level of community transmission in Australia, routine use of COVID-19 vaccines during pregnancy is not currently recommended by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists.[7] However, it states that vaccination may be considered in some groups with a high risk of complications from COVID-19. The guidelines also recommend that pregnant healthcare workers in an at-risk work environment should be allocated to lower risk duties, work from home or take leave of absence. If avoiding exposure is not possible, they should be offered vaccination. The Australian Department of Health has published a guide to help women making decisions about vaccination during pregnancy and breastfeeding.

The vaccine is supplied in multidose vials that should be stored in the refrigerator (2–8°C). Each vial contains ten 0.5 mL doses. Dilution of the vial is not required before administration. A separate sterile needle and syringe should be used for each patient. Opened vials should be discarded after six hours at room temperature and after 48 hours if stored in the refrigerator.

The vaccine should be given by intramuscular injection, preferably in the deltoid muscle. Two separate 0.5 mL doses should be given 4–12 weeks apart. The patient's name and the batch number of the vaccine must be recorded in the Australian Immunisation Register. Enhanced monitoring of adverse events following immunisation is in place for the COVID-19 vaccines at national and state and territory levels.[2] Training modules for vaccination providers have been developed by the Department of Health in partnership with the Australian College of Nursing to ensure COVID-19 vaccines are handled and administered safely.

This vaccine appears to be well tolerated and is effective at preventing COVID-19. Vaccine efficacy in older people and protection against variant SARS-CoV-2 strains is currently unclear. Follow-up data are limited so the duration of protection is also not yet known but clinical trials are ongoing. This vaccine is indicated for adults only.

Although the Australian Government's COVID-19 vaccination plan is for vaccines to be universally available, free and voluntary, they are initially being rolled out to priority groups including quarantine and border workers, frontline health workers, and staff and residents in aged care. Other vulnerable groups and high-risk workers are being targeted in later phases before the vaccine is rolled out to everyone.

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[X] manufacturer did not respond to request for data

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

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NEW DRUGS

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Cinnarizine/dimenhydrinate

Approved indication: vertigo

Cizinate (Southern Cross)
20 mg/40 mg tablets

Vertigo has a variety of causes. These may be peripheral, such as labyrinthitis, or central, such as cerebellar ischaemia, or a mixture of the two. The treatment of vertigo should be aimed at the cause, but a variety of drugs has been used to relieve the symptom. These include antihistamines, anticholinergics and antiemetics.

The combination product contains two antihistamines. Cinnarizine inhibits histamine H_1 and H_4 receptors and dopamine D_2 receptors. It can also block calcium channels. Dimenhydrinate is a salt of diphenhydramine and chlorotheophylline. It inhibits histamine H_1 receptors and muscarinic acetylcholine receptors and can enter the brain. The combination of cinnarizine and dimenhydrinate will therefore have peripheral and central effects.

After oral administration, diphenhydramine is released from dimenhydrinate. Diphenhydramine and cinnarizine are rapidly absorbed with peak plasma concentrations being reached in 2–4 hours. They are metabolised mainly by cytochrome P450 (CYP) 2D6 in the liver. There may be a potential to interact with other drugs metabolised by CYP2D6, such as antidepressants and beta blockers. The half-lives of the drugs vary with the age of the patient but are around 4–6 hours. Cinnarizine and its metabolites are mainly excreted in the faeces, while diphenhydramine and its metabolites are mainly excreted in the urine. The combination is therefore contraindicated in patients with severe hepatic or renal impairment.

The combination of cinnarizine and dimenhydrinate has been used in Europe for many years, so there are several studies of its efficacy. An analysis of five of the double-blind, randomised trials involved 635 patients with an average age of 53 years. Most of them had experienced vertigo for more than one year. A total of 196 patients took the combination, while the others took either cinnarizine, dimenhydrinate or betahistine. The drugs were taken three times a day for four weeks. According to a symptom rating scale (range 0–40), the patients' symptoms decreased by more than 70% with the combination. This decrease was greater than the decrease seen with the components given alone (see Table). More than 68% of the patients felt much improved or very much improved after taking the combination compared with 33% of the betahistine group and 35% of the placebo group.[1]

A more recent double-blind trial compared the combination to betahistine in 306 patients with peripheral vestibular vertigo. Approximately 55% of the patients had a Ménière-like symptom complex, but patients with confirmed Ménière's disease were excluded. A 12-item scale was used to calculate a mean vertigo score. After four weeks this composite score had declined by 67.5% in the patients taking the combination and by 59.5% in those taking betahistine. Approximately 71% of the 152 patients randomised to the combination felt much improved or very much improved compared with 63% of the betahistine group.[2]

In the analysis of five trials, the most frequent adverse effects seen with the combination of cinnarizine and dimenhydrinate were fatigue, somnolence, dry mouth, headache and abdominal pain. The sedative effects may be increased by other drugs, including alcohol, which depress the central nervous system. As the combination has some anticholinergic effects, it is contraindicated in patients with angle-closure glaucoma or urinary retention. Convulsions, raised intracranial pressure and

Table **Efficacy of cinnarizine/dimenhydrinate for vertigo**[1]

	Number of patients (intention to treat)	Mean reduction in vertigo score after four weeks (range 0–40)
Cinnarizine 20 mg/dimenhydrinate 40 mg	196	13.6
Cinnarizine 20 mg	60	11.5
Cinnarizine 50 mg	98	7.8
Dimenhydrinate 40 mg	59	11.4
Dimenhydrinate 100 mg	97	7.3
Betahistine 12 mg	40	5.7
Placebo	51	6.4

alcohol abuse are also contraindications. Cinnarizine has been associated with extrapyramidal effects including tardive dyskinesia. As these effects may be irreversible, the combination should only be used for short-term management.

Combining cinnarizine with dimenhydrinate has a greater effect on vertigo than either drug alone, but the difference may be small. For example, in the five-trial analysis there was a difference of approximately two points between the combination and cinnarizine 20 mg on the 40-point vertigo score (see Table).[1] However, cinnarizine is not available on its own in Australia. Although there is European experience with the combination, it is only indicated in Australia for adults who have not responded to other treatments. In view of the uncertainty about long-term safety, treatment should not usually exceed four weeks.

T manufacturer provided the product information

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

NEW DRUGS

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Defibrotide

Approved indication: hepatic veno-occlusive disease

Defitelio (Link Medical)
vials containing 200 mg/2.5 mL concentrate for dilution

Haematopoietic stem cell transplants can improve survival in patients with certain cancers, such as acute leukaemia. However, the procedure has many risks. One of the complications of haematopoietic stem cell transplantation is hepatic veno-occlusive disease, also known as sinusoidal obstruction syndrome. This results from damage to the endothelial cells in the liver. In addition to liver dysfunction, there may be failure of other organs. If untreated, the mortality rate in severe cases exceeds 80%.

Although the mechanism of action is uncertain, defibrotide has antithrombotic and anti-inflammatory effects. It may protect endothelial cells from damage.

Defibrotide is a mixture of oligonucleotides derived from the intestinal mucosa of pigs. It is supplied as a concentrate which has to be diluted before being given as an intravenous infusion over two hours. The dose is determined by the patient's weight.

After the infusion, defibrotide is rapidly cleared and will no longer be detectable within 3.5 hours. The infusion has to be repeated every six hours for a minimum of 21 days. Most of the dose is metabolised then excreted in the urine. Although plasma concentrations will be increased in patients with renal impairment, no dose adjustment is recommended.

A phase II trial studied two dosing regimens in 151 patients with severe hepatic veno-occlusive disease. They were given infusions every six hours for a median duration of approximately 20 days. Among the 72 patients who received 25 mg/kg/day there was a decrease in bilirubin and resolution of organ dysfunction in 49%. There were 44% who survived for at least 100 days after their stem cell transplant.[1]

The 25 mg/kg/day regimen was used in a phase III trial of severe veno-occlusive disease and multiorgan failure in 102 adults and children. Defibrotide was infused for a median of 21.5 days. There was a complete response in 25.5% of the patients, which was greater than the 12.5% response rate in a group of historical controls. The median time to a complete response to defibrotide was 34.5 days. At 100 plus days after their stem cell transplant 38.2% of this group was alive compared with 25% of the historical controls.[2]

An analysis of 573 patients treated in an expanded access program supported the clinical trial results. In the 387 patients with veno-occlusive disease and multiorgan dysfunction the survival rate was 45% at 100 plus days after transplant. This post hoc analysis suggested earlier treatment increased the chance of survival.[3]

In patients with severe veno-occlusive disease following stem cell transplantation, adverse events are common and so it can be difficult to be certain which are caused by treatment. During the phase III trial approximately 11% of the patients stopped defibrotide because of possible toxicity. Common adverse events include hypotension, vomiting, diarrhoea, fever, peripheral oedema and respiratory failure. The antithrombotic and fibrinolytic effects of defibrotide may contribute to cases of bleeding including epistaxis, haematuria and pulmonary alveolar haemorrhage. There is likely to be an interaction with other drugs that affect clotting.

There are difficulties in conducting clinical trials in seriously ill patients with veno-occlusive disease. The phase III trial was open label and not randomised. There were only 32 patients in the historical control group. While more patients given defibrotide survived for 100 plus days, there was little difference from the historical controls at 180 plus days (32.4% vs 25%).[2] Despite these methodological limitations, it does appear that defibrotide can improve short-term survival in patients with severe hepatic veno-occlusive disease after haematopoietic stem cell transplant.

[X] manufacturer did not respond to request for data

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

Ozanimod

Approved indication: multiple sclerosis

Zeposia (Celgene)
230, 460 and 920 microgram capsules

The pathophysiology of multiple sclerosis is thought to involve the migration of lymphocytes into the central nervous system. This has led to drugs that alter the immune system being used in the management of patients with multiple sclerosis. In the 1990s interferons were used, followed by injectable monoclonal antibodies, such as alemtuzumab, in the 2000s. Later, oral drugs such as fingolimod were developed.

Like fingolimod, ozanimod is aimed at the sphingosine 1-phosphate (S1P) receptors on the surface of lymphocytes. By binding to these receptors ozanimod is thought to reduce the migration of lymphocytes into the central nervous system.

After absorption ozanimod is extensively metabolised. The parent molecule only accounts for about 6% of the drug activity in the circulation with the rest being accounted for by active metabolites. The multiple enzyme systems involved in the metabolism of ozanimod include cytochrome P450 (CYP) 3A4 and CYP2C8 and monoamine oxidase. There are many potential pharmacokinetic interactions and drugs such as rifampicin and monoamine oxidase inhibitors should be avoided. Ozanimod should not be used in patients with severe liver disease. As little ozanimod is excreted in the urine, it can be used in patients with renal impairment. The half-life of ozanimod is 21 hours, but it is several days for the main metabolites. The long half-life enables a once-daily dose.

The main double-blind clinical trials of ozanimod studied adults up to 55 years old with relapsing forms of multiple sclerosis (see Table).[1,2] These patients were randomised to receive oral ozanimod 0.5 mg or 1 mg daily, or weekly injections of interferon beta-1a. The primary outcome of the trials was the annualised rate of relapse. Brain lesions were evaluated by MRI and disability was assessed using the Expanded Disability Status Scale.[1,2]

In the SUNBEAM trial, 1346 patients were randomised and treated for an average of about 13.5 months. Approximately 93% of the patients completed the study. The annualised relapse rate was 0.24 with ozanimod 0.5 mg and 0.18 with ozanimod 1 mg. These rates were lower than the rate of 0.35 with interferon beta-1a. The number of new or enlarging lesions seen on MRI was also lower with ozanimod.[1]

The RADIANCE trial randomised 1320 patients and treated them for two years. Approximately 87% completed the study. The annualised relapse rate following treatment with interferon beta-1a was 0.28, compared with 0.22 for ozanimod 0.5 mg and 0.17 for ozanimod 1 mg. There were fewer new or enlarging lesions in the brains of the ozanimod group compared to the interferon group.[2]

Adverse events were common in the clinical trials. Approximately 3% of the patients taking ozanimod 1 mg stopped the drug because of these events.[1,2]

Treatment with ozanimod reduces the number of lymphocytes in the circulation. This increases the risk of infection. In the 24-month trial infections such as nasopharyngitis and urinary tract infection were more frequent with ozanimod than with interferon.[2] As herpes zoster was also more frequent, varicella zoster vaccine is recommended for non-immune patients at least one month before starting ozanimod. Live vaccines should not be used during treatment or for three months afterwards.

In addition to checking the patient's full blood count, liver function should be monitored. An increase in liver

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Related article:
Siponimod for multiple sclerosis

Table **Efficacy of ozanimod in relapsing multiple sclerosis**

Trial	Patient allocation	Mean number of relapses in the year before treatment	Annualised relapse rate with treatment
			At 12 months
SUNBEAM[1]	448 interferon beta-1a	1.3	0.35
	451 ozanimod 0.5 mg	1.3	0.24
	447 ozanimod 1 mg	1.3	0.18
			At 24 months
RADIANCE[2]	443 interferon beta-1a	1.3	0.28
	443 ozanimod 0.5 mg	1.4	0.22
	434 ozanimod 1 mg	1.3	0.17

enzyme concentrations to five times the upper limit of normal was an indication to stop ozanimod in the clinical trials.

Drugs acting on the S1P receptor can cause bradycardia. An ECG is required before treatment and ozanimod is contraindicated if the patient has heart block or a recent history of cardiovascular events such as stroke or myocardial infarction. To reduce the risk of bradycardia the dose of ozanimod is titrated, to the recommended dose of 920 micrograms once daily, over eight days.

Some patients, such as those with diabetes, may be at increased risk of macular oedema while taking ozanimod. They should have ophthalmological examinations before and during treatment.

Animal studies found ozanimod was teratogenic. It should not be used in pregnancy, so women who could become pregnant should use effective contraception during treatment and for three months afterwards. Ozanimod should also not be used during lactation.

When efficacious treatments are available, it would probably not be ethical to compare ozanimod with a placebo, however interferon may not be the most appropriate comparator. While treatment with ozanimod had a larger effect on the rate of relapse, it did not have an advantage over interferon in the progression of disability.[2]

The more selective action of ozanimod on S1P receptors might give it a possible advantage over fingolimod. For example, a patient starting fingolimod requires cardiac monitoring for bradycardia over at least six hours. This is not required with ozanimod, but monitoring is also not needed with siponimod, another recently approved S1P receptor modulator.

Until there is more experience with the new oral drugs it will be uncertain if they have the same risk of rare, but serious, adverse reactions such as the cancers and progressive multifocal leukoencephalopathy seen with fingolimod.

T manufacturer provided the product information

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Selexipag

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Approved indication: pulmonary arterial hypertension

Uptravi (Actelion)
200, 400, 600, 800, 1000, 1200, 1400 and 1600 microgram film-coated tablets

An increase in the pulmonary artery blood pressure may be idiopathic or related to conditions such as congenital heart disease, connective tissue disease or chronic obstructive pulmonary disease. Pulmonary arterial hypertension leads to right ventricular dysfunction. Patients with pulmonary arterial hypertension can be classified according to how much it limits their activity. The median survival in the highest class (IV) is only about six months.

Several signalling pathways are involved in the pathophysiology of pulmonary arterial hypertension and are therefore the target of drug therapy. For example, bosentan is an endothelin antagonist, sildenafil acts on the nitric oxide pathway, while epoprostenol is an agonist at the prostacyclin receptor. Stimulating this receptor causes vasodilation.

Epoprostenol requires intravenous infusion while iloprost, another prostacyclin analogue, needs to be nebulised. There was therefore a need for a more convenient way to act on the prostacyclin pathway.

Selexipag is a prostacyclin receptor agonist but has a different structure from the prostacyclins and it can be given by mouth. After it is absorbed selexipag is hydrolysed to an active metabolite. The drug and its metabolite have antiproliferative and antifibrotic effects in addition to vasodilation. As the metabolism of selexipag involves several enzyme systems, including cytochrome P450 and the glucuronosyltransferases, there is a potential for pharmacokinetic interactions, but their clinical relevance is unclear. Concentrations of selexipag and its active metabolite increase with decreasing liver function. The drug should not be used in patients with severe hepatic impairment. Most of the metabolites are excreted in the faeces.

In a phase II trial 43 patients being treated for pulmonary arterial hypertension were randomised to add selexipag or a placebo. The dose was increased over several weeks and the effect was assessed after 17 weeks. In the 33 patients given selexipag, pulmonary vascular resistance declined to 80.7% of its baseline value. As resistance increased in the placebo group, the outcome was effectively a 30.3% reduction in the mean pulmonary vascular resistance.[1]

A phase III placebo-controlled trial studied 1156 patients with pulmonary arterial hypertension that was either idiopathic, heritable, or associated with connective tissue disease, repaired congenital shunts, HIV, drug use or exposure to toxins. The trial enrolled some untreated patients, and excluded patients treated with prostacyclins. The dose was titrated over 12 weeks to an individualised maintenance dose. The 574 patients randomised to receive selexipag continued it for a median of 70.7 weeks, while the other 582 patients took a placebo for a median of 63.7 weeks.[2]

The primary end point of the trial was death or a complication of pulmonary arterial hypertension. These events occurred in 27% of the selexipag group and 41.6% of the placebo group. This reduction was seen in untreated and previously treated patients.[2]

In the phase III trial 14.3% of the patients stopped selexipag, compared with 7.1% of the placebo group, because of adverse effects. They were more likely to experience symptoms such as headache, pain in the jaw, nausea, vomiting and diarrhoea. As selexipag causes vasodilation some patients may develop hypotension, and there can be an increase in heart rate. Selexipag is therefore contraindicated in patients with severe arrhythmia, coronary heart disease, decompensated heart failure or a recent history of myocardial infarction or cerebrovascular events. Although selexipag can inhibit the aggregation of platelets, it did not increase the risk of bleeding. In the phase III trial anaemia and hyperthyroidism were more frequent with selexipag than with placebo. Selexipag may also cause pain in the extremities, myalgia and eye pain.[2]

All patients will experience adverse effects because the recommended regimen is to titrate the dose until the patient cannot tolerate the drug or the dose reaches 1600 micrograms twice daily. In the phase III trial only about 43% of the patients could be maintained on higher doses (1200–1600 micrograms).[2]

Most of the patients in the trial were already being treated and adding selexipag appeared to only have a small effect on disease progression. From a baseline of 353 m, the distance patients could walk in six minutes increased by a median of 4 m following treatment with selexipag. In the placebo group there was a decrease of 9 m. While selexipag had an advantage over placebo in the phase III trial its effect on survival is uncertain. There were fewer hospitalisations for worsening pulmonary arterial hypertension, but more patients died (4.9% vs 3.1%).[2] Despite these limitations, the oral route of administration is likely to see selexipag being used in the management of pulmonary arterial hypertension.

T manufacturer provided relevant information

NEW DRUGS

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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.

Siponimod

Aust Prescr 2021;44:69–70
https://doi.org/10.18773/austprescr.2021.014

Related article:
Ozanimod for multiple sclerosis

Approved indication: multiple sclerosis

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Most patients with multiple sclerosis have relapses and remissions, however some will eventually develop a progressive form of the disease. While there are several options available for relapsing-remitting disease, there are no effective drugs for secondary progressive multiple sclerosis.

Almost a decade ago, fingolimod was approved for use in patients with relapsing forms of multiple sclerosis to reduce the frequency of relapses and delay the progression of disability. Like fingolimod, siponimod binds to sphingosine-1-phosphate (S1P) receptors, but to a different range of receptor types ($S1P_1$ and $S1P_5$). These receptors are found on T lymphocytes and blocking them reduces the entry of T cells into the central nervous system. This reduces the inflammation which contributes to the progression of multiple sclerosis.

The daily dose is well absorbed irrespective of food. This metabolism is highly susceptible to inter-individual differences in cytochrome P450 (CYP) activity. CYP2C9 is the main enzyme involved, followed by CYP3A4. Pharmacokinetic interactions are therefore possible with inducers (such as carbamazepine) and inhibitors (such as fluconazole) of these enzymes. Siponimod has a half-life of 30 hours and most of the dose is excreted as metabolites in the faeces. No dose adjustments have been recommended for patients with liver or kidney disease. In pregnancy, animal studies show that siponimod can harm the fetus.

A phase II dose-ranging trial studied siponimod in 297 patients with relapsing-remitting multiple sclerosis. This found that siponimod reduced the number of lesions seen on MRI scans. For example, after three months of treatment with siponimod 2 mg daily there was a relative reduction of 70% compared to placebo. That dose reduced the annualised rate of relapse to 0.2 compared to 0.58 with placebo.[1]

The 2 mg dose was used in the main phase III trial in secondary progressive multiple sclerosis. This trial recruited patients with moderate–advanced disability. Approximately 60% of the patients were women. One group of 1100 patients took siponimod while 546 were randomised to placebo. The primary outcome of this trial was the progression of disability. This was assessed using the Expanded Disability Status Scale (a higher score indicates increasing disability). At the start of the study the mean score on the 10-point scale was 5.4. This increased (by 0.5 or 1.0 points depending on the patient's baseline score) in 32% of the placebo group and 26% of the siponimod group. MRI showed a smaller increase in the volume of lesions seen in patients taking siponimod. Their brain volumes also reduced at a lower rate than in the placebo group. The annualised relapse rates were 0.07 with siponimod and 0.16 with placebo.[2]

The median time patients participated in the phase III trial was 21 months. Adverse events resulted in 8% of the siponimod group and 5% of the placebo group stopping treatment. There were four deaths in each group. Adverse events that were more frequent with siponimod included abnormal liver function, hypertension, peripheral oedema, macular oedema, bradyarrhythmia and convulsions.[2]

The mechanism of action of siponimod results in fewer peripheral lymphocytes. This can increase the risk of infection and this hazard may persist for up to a month after treatment stops. In the phase III trial, the overall incidence of infections (49%) was not different from placebo, but herpes viral infections, including shingles, were more frequent with siponimod.[2] Patients without antibodies should be given varicella vaccine before starting siponimod. Live vaccines should be avoided.

The bradyarrhythmia associated with siponimod is seen at the start of treatment. An ECG is needed before treatment begins and the dose of siponimod must be titrated over several days. It should not be used in patients with conduction problems such as second degree (Mobitz type II) heart block.

An ophthalmological examination is recommended before treatment. In view of the risk of macular oedema, further examination is needed if there is a change in vision.

Siponimod is also contraindicated in patients with particular CYP2C9 genotypes. Genetic testing is therefore required before treatment.

At this stage there is limited evidence about the effectiveness of siponimod in preventing disability in secondary progressive multiple sclerosis. What impact will outcomes such as a 0.15% difference in decreased brain volume have on long-term disability? While there was a statistical advantage in changes on the EDSS score, there was no clear benefit in mobility. The time taken for patients to walk 25 feet (7.6 m) increased by at least 20% in 40% of the siponimod group and 41% of the placebo group. There was also no statistically significant difference on the Multiple Sclerosis Walking Scale. Subgroup analysis of the patients in the phase III trial suggests siponimod has less effect in older people, those with a long history of multiple sclerosis and those with higher levels of disability.[2]

T manufacturer provided the AusPAR

NEW DRUGS

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ANSWERS TO SELF-TEST QUESTIONS

1 False 2 True

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