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CONTENTS

ARTICLE

Suicidality: prevention, detection and intervention

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antidepressants, depression, drug overdose, suicide

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SUMMARY

Australian suicide rates are increasing. GPs have a key role in the early detection and management of suicidality and the treatment of commonly associated mood disorders and substance misuse.

Drugs are indicated for moderate to severe depression. They can also be considered for patients who have been unable to access, do not want or have not responded to psychological treatments.

Selective serotonin reuptake inhibitors are less toxic than serotonin noradrenaline reuptake inhibitors. Tricyclic antidepressants are the most dangerous in overdose. Mood stabilising drugs can be prescribed, but in large quantities they are dangerous in overdose.

In depressed adolescents psychological therapies are first-line treatments. When drugs are indicated, in older people selective serotonin reuptake inhibitors are generally well tolerated, but paroxetine and fluoxetine are best avoided.

Introduction

Suicide accounts for 1.4% of all deaths worldwide.[1,2] In Australia, suicide is the leading cause of death among those aged 16–24 years, while the suicide rates in men aged over 85 years are the highest for any age group.[3] In 2015, 3027 Australians died by suicide, more than the national road toll.[3] In 2006 the death rate from suicide was 10.2 per 100 000 people. This rose to 12.6 per 100 000 in 2015.[3] For every death by suicide, around 25 people will attempt suicide[4] and many more will engage in non-suicidal self-injury (such as self-cutting). Self-injury is associated with a greater likelihood of suicidal thoughts and behaviours.[5]

Prevention

Suicide results from a convergence of genetic, biological, psychological, social and cultural factors often combined with an experience of trauma and loss.[1] Despite the rising toll, suicide is still a comparatively rare event. Given the complexity of its causation, it is unsurprising that no single suicide prevention strategy clearly stands out above the others.[1,2] These facts also explain the counterintuitive finding that no single risk factor that is statistically significantly associated with an increase in suicide – such as a history of self-harm or depressed mood – provides any practical assistance in predicting which particular patients might take their own life.[1,6,7] Prevention strategies therefore need to be multifactorial and tailored to the individual patient.

There are suicide risk assessment tools, but these should be used as guides only and not as replacements for clinical decision making.[8,9]

Suicide prevention is most likely to be effective if a combination of evidenced-based strategies are used both at the individual and population levels.[1,4]

One of the strongest evidence-based strategies for suicide prevention is the education of primary care clinicians.[10] In Australia, GPs are the most frequent providers of mental health care and many patients who attempt suicide visit their GP in the preceding months.[11] This makes GPs well placed to help reduce the rate of suicide. Doctors should remember that a therapeutic relationship can be protective.[12-14]

The approach to the suicidal patient

Most suicidal patients will be distressed and many will feel stigmatised and ashamed. Clinicians should offer comfort, reassurance and hope, and avoid judgement.[15] When a patient admits to suicidal thoughts or behaviour, understanding their predicament begins with an exploration of these phenomena (Box 1). This includes the nature of the thoughts or behaviours, any plans, previous suicide attempts and access to means of harm, for example firearms, poisons, and medicines that are dangerous in overdose such as quetiapine, opioids and tricyclic antidepressants. The clinician should then review the circumstances that might be contributing to the patient's suicidality (Box 2).

Management plans should be negotiated with the patient. In most cases family, friends or other psychosocial supports should be involved.[15]

A key element of any management plan will be to consider the least restrictive environment for safely starting treatment. Most patients can be managed

in the community. However, if in doubt (because, for example, the burden of stressors threatens to overwhelm the patient, or if psychosocial supports are unavailable), obtaining a second opinion about whether hospitalisation is necessary through the local acute mental health team, or the emergency department, is sound clinical practice. Patients whose severe depression or psychotic symptoms make them unable to cooperate with community treatment can be compelled to have such an assessment under mental health legislation.

All management plans include reinforcement of protective factors including the involvement of family and friends where possible, provision of emergency contacts, formulation of an individualised self-care plan and encouragement to avoid alcohol and other substances (which increase impulsivity). Every suicidal patient should be seen at least weekly until the acute crisis resolves. Good communication between care providers is essential.

Substance use and depression

Substance misuse (especially alcohol) is a common method of self-medication for depression and anxiety, but it increases the likelihood of suicidal behaviour. The patient's substance use must be explored in the assessment and addressed in the management plan.

Patients should be encouraged to stop drinking alcohol. Motivational interviewing is the first-line intervention for alcohol misuse. Many online treatments for depression (such as MyCompass at www.mycompass.org.au) use motivational interviewing principles to help people begin to address substance misuse. Several online treatments specifically for alcohol misuse are currently being developed and evaluated including Shade (www.shadetreatment.com), Daybreak, Hello Sunday Morning (www.hellosundaymorning.org) and OnTrack Alcohol and Depression (www.ontrack.org.au).

Early intervention in depression

Patients appreciate their GP asking about their mental health, although they may not volunteer psychological symptoms. Consider psychological causes when patients present with physical symptoms that are trivial or for which no underlying cause is evident, especially when there is no positive response to reassurance. GPs should be alert to body language or other cues suggesting an underlying mood disorder.

Around 5% of adults will experience an episode of major depressive disorder each year.[16] GPs who wish to assess patients for the symptoms and severity of depression (and associated anxiety) may use well-validated, self-report scales such as the Patient Health Questionnaire (PHQ-9) or the Generalised Anxiety Disorder 7 (GAD7).[17-19] The Patient Health Questionnaire includes a question regarding suicidality which can be a useful springboard for further discussion.[20]

Early and successful treatment can significantly reduce the length and severity of episodes of depression and associated suicidal thoughts or behaviour. Patients with mild–moderate depression will often respond to psychological therapies. These include cognitive behaviour therapy or interpersonal psychotherapy and may be delivered face-to-face, or via self-guided or clinician-assisted evidence-based

Box 1 Questions to assess a patient's suicidality

Tell me about your thoughts of suicide – what goes through your mind?

How long have you had these thoughts?

How often do you have them?

Do you find it hard to push these thoughts away?

Do you think you would carry out these thoughts?

Have you made any plans to suicide? If so, what are they? (Consider access to especially lethal means, such as firearms, medicines or hanging).

Have you ever tried to commit suicide in the past? If so, what happened?

Who is important to you? Do they know how you have been feeling?

If you could change a couple of things in your life, what would they be?

Do you have any ideas, things that you may have tried in the past, that could help you feel differently/better?

How can I help?

Box 2 Factors contributing to suicidal thoughts

Bereavement

Relationship problems

Non-adherence to treatment

Increased alcohol or other drug use or established dependence

Depressive illness

Other existing mental illnesses (recent discharge from a psychiatric unit is a time of higher risk)

Chronic pain or physical illness

History of severe psychological trauma

Loss of hope

Loss of support

e-mental health interventions (Box 3). Patients with moderate–severe depression are likely to also require antidepressants as may those who have not benefited from psychological therapies or cannot or do not want to access them.[20]

Psychological therapy

There is much evidence that psychological therapies can reduce suicidality and promote well-being in all age groups and across a range of diagnoses including depression, bipolar disorder, schizophrenia and borderline personality disorder.[1]

In adolescents, multisystem and family-based treatments are effective.[1] Family-focused interventions are invariably necessary in the treatment of the depressed adolescent. These may include psycho-education and support for parents, family therapy or the treatment of mental illness in a parent. School-based interventions focusing on mental health literacy, suicide risk awareness and skills training (in dealing with adverse life events and stress) can reduce suicidal thinking and attempts, including at 12-month follow-up.[1]

Ongoing collaborative care, especially involving specialist mental health and primary healthcare services, has been shown to be feasible, acceptable and effective in reducing suicidal ideation compared to standard care in the general adult population. Similar programs for depressed and suicidal older patients are also effective.[1]

Choosing an antidepressant

The choice of antidepressant must consider individual patient factors such as age (Box 4[21,22] and Box 5). It is also guided by efficacy, tolerability, the prominence of certain symptoms, the depressive subtype, adverse effects, the potential for drug–drug interactions and the drug's safety in overdose.

Suicidality

There is no specific drug for preventing suicide, although antidepressants reduce the intensity of suicidal thoughts over time in depressed patients. It has been suggested that antidepressants could increase the risk of suicide, but this is unlikely (Box 6).[20,23-30]

Danger in overdose

Tricyclic antidepressants, particularly dothiepin, are the most dangerous of the antidepressants in overdose, followed by serotonin noradrenaline reuptake inhibitors (desvenlafaxine is less toxic then venlafaxine) and then others such as mirtazapine. Selective serotonin reuptake inhibitors are the least dangerous, although citalopram and escitalopram have a significant risk of seizures and QT prolongation[31] and fluoxetine has a long half-life.

Box 3 Examples of e-mental health interventions

myCompass – free, with a pre-registration overview
www.mycompass.org.au

This Way Up – registration and a small fee are required
https://thiswayup.org.au

MindSpot – free, GP referral required
www.mindspot.org.au

Box 4 Antidepressants for adolescent depression

Fluoxetine is recommended by National Institute for Health and Care Excellence (UK) and Beyond Blue for the treatment of depression in young people when psychological therapies (such as cognitive behaviour therapy or interpersonal psychotherapy) are refused, unavailable, or ineffective, and when symptoms are severe.[21,22]

Starting fluoxetine (or another selective serotonin reuptake inhibitor) can cause a temporary increase in anxiety or agitation which may be associated with an increase in suicidal ideation or self-harming behaviour.

While unwanted effects can be minimised with a 'start low, go slow' dosing strategy, young people and their families should be warned of a possible increase in suicidality when starting antidepressants. They should be encouraged to report this immediately to their parents, or their doctor.

Fluoxetine has a long half-life and can therefore be ceased abruptly if required.

Young patients starting an antidepressant should be seen at least weekly until the severity and suicidality, if present, are no longer of clinical concern.

If suicidal patients require an antidepressant, we recommend using a drug which is less toxic and that only a week's supply be prescribed (or dispensed) at a time.

Mood stabilisers

Lithium can significantly reduce the incidence of suicide attempts and completed suicide in patients with major mood disorders, compared to those not treated with lithium.[16,32]

Lithium, valproate, carbamazepine and lamotrigine are dangerous in overdose and lethal quantities may be available on a single prescription.

Antipsychotics

Clozapine has been reported to be more effective than olanzapine in the treatment of suicidality in patients with schizophrenia and schizoaffective disorder.[33]

Box 5 Antidepressants for suicidal older people

People in late life are more likely to have chronic physical illness, experience pain, be isolated and be bereaved, all of which contribute to suicidality. Depression in older people is undertreated and the incidence of suicide is high.

The choice of antidepressant should be based on the optimal adverse effect profile and the risk of drug–drug interactions. Due to the metabolic changes of ageing, older patients are at a greater risk of potentially fatal toxicity and drug–drug interactions when they deliberately or inadvertently take larger quantities of antidepressants.

Most of the selective serotonin reuptake inhibitors (SSRIs) and mirtazapine, moclobemide and desvenlafaxine are relatively safe in older people. Having fewer anticholinergic effects than other antidepressants, these drugs are well tolerated by patients with cardiovascular disease and are less likely to impair cognition, cause constipation or lead to urinary retention.

When considering SSRIs avoid paroxetine which has the most anticholinergic adverse effects and fluoxetine which has a long half-life.

Box 6 Do antidepressant drugs cause suicide?

A meta-analysis of trial data submitted to the US Food and Drug Administration (FDA) confirmed that suicidal behaviour did not differ between those taking placebo and those taking antidepressants.[23]

There is strong evidence that the risk of suicide is highest in the month before starting an antidepressant, declines quickly during the first week of treatment, and steadily decreases to even lower, stable rates with continued treatment.[24]

A number of epidemiological studies over the last several decades have shown an inverse relationship between the number of prescriptions for antidepressants and the frequency of suicides.[25]

The FDA black box warning in 2004 cautioned prescribers about an increase in suicidal thinking and behaviour (although not successful suicides) in young people prescribed antidepressants. However subsequently several studies[26-28] have shown an inverse relation between successful suicide and antidepressant prescribing in this age group.

Overall, in children and adolescents with depression, the evidence does not support avoiding antidepressants because of an increased risk of suicidal behaviour. The Treatment for Adolescents with Depression Study found that cognitive behaviour therapy plus fluoxetine might lead to less suicidal ideation and behaviour than just fluoxetine alone.[29,30]

Source: Adapted from reference 20

Conclusion

For depression and substance misuse, psychological therapies and drugs are key components of treatment. Drugs are especially important for moderate to severe depression. With an empathic approach and awareness of which drugs are most efficacious, tolerable and least dangerous in overdose, GPs are well placed to intervene early to prevent or reduce suicide. <

In the past three years Henry Brodaty has been on an advisory committee for Nutricia. He is a consultant for Eli Lilly and Lundbeck in the field of dementia and his centre has been funded to undertake trials for Alzheimer's disease by Tau Therapeutics, Servier and Sanofi.

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Q:

SELF-TEST QUESTIONS

True or false?

1. Antidepressants increase the rate of suicide in severely depressed adolescents.
2. Lithium reduces the risk of suicide in patients with mood disorders.

Answers on page 203

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Letters to the Editor

Drugs and genetics

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I read with interest two excellent articles in the June 2017 issue. One described the main pharmacogenomic tests available in Australia and their relevance to clinical practice.[1] The other highlighted concerns with direct-to-consumer genetic testing, particularly the over-enthusiastic promotion and difficulties in actioning test results.[2]

Understanding why a patient has a specific response to a medicine is complex and dependent on the dynamic interplay of many intrinsic and extrinsic factors. To consider pharmacogenomics in isolation is like reading one section of a book and expecting to know the story. Very rarely, the critical part is read and the story recounted well. This is analogous to the avoidance of abacavir hypersensitivity with HLA-B*5701 testing[1] or cures with targeted pharmacotherapy in oncology.[3] Mostly, pieces of valuable information are cobbled together, blanks are filled in based on assumptions, and a good story is told to an interested listener. However, then the story becomes equivocal with pressure testing. This is comparable to mainstreaming of 'precision medicine', the over-enthusiastic promotion of direct-to-consumer genetic testing, and the fights between pharmacogenomic and medical experts about clinical value and implementation.

For those expecting a simple answer to the complexity of predicting a patient's response to treatment, pharmacogenomics has failed. For those who are realistic about its limitations, pharmacogenomics is just one of several components required for more advanced approaches that predict medication response, such as quantitative systems pharmacology[4] and physiologically based pharmacokinetics and dynamics.[5]

As well as improved pharmacogenomics education, skills in assessing the clinical relevance of variability in drug action more broadly are also needed among clinicians. Otherwise, innovative technologies claiming to improve prescribing in the future will not receive the thorough evaluation necessary to protect patients, their health and their hip pockets.

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ARTICLE

Medication management on sick days

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acute disease, adverse drug reaction, chronic kidney disease, contraception, diabetes, drug interactions

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CPD FOR PHARMACISTS

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SUMMARY

Patients may be susceptible to adverse drug events during acute illness due to comorbidities or medicine use. Acute illness should prompt careful monitoring or dose adjustment in patients prescribed certain medicines.

Patient factors, severity and expected duration of illness, and class of drug should be considered to minimise the risk of adverse drug events.

Some drugs may need to be temporarily suspended, such as metformin, diuretics and sodium-glucose co-transporter 2 inhibitors when there is a risk of hypovolaemia.

Those with chronic kidney disease are at risk of acute kidney injury due to limits in their physiological reserve. This may be compounded by medicine use.

Temporary increases in dose may be required for insulin and corticosteroids.

Withdrawal syndromes may occur with controlled-release drugs, such as dopamine agonists, antidepressants and analgesics, due to malabsorption.

An action plan may be needed for medicine use on sick days. Patient education around supplemental dosing of oral contraceptives to maintain efficacy after acute illness is important.

Introduction

During intercurrent illness, the risk of an adverse drug event could be increased by ongoing use of some medicines. They may cause harm with either continued use or abrupt cessation during illness. For example, ongoing use of an antihypertensive on sick days may compound hypotension associated with the acute illness. Factors to consider for dose adjustment include the type of medicine, formulation and pharmacokinetics, duration of illness and comorbidities.

Pathophysiology

An understanding of pharmacokinetic factors associated with significant illness (sick days) can be useful to predict and manage patients at most risk. Changes in drug absorption, distribution, metabolism and excretion are well documented in critically ill patients. Unfortunately, there are less data to guide the prescribing of regular medicines in less severe illness. Common symptoms that could indicate a patient is at risk of hypovolaemia include anorexia, diarrhoea, vomiting and fever. Depending on the severity of illness and the susceptibility of the patient, volume depletion and renal dysfunction can occur. This can impair the excretion of medicines and result in accumulation and toxicity. Severe gastroenteritis may decrease the bioavailability due to reduced gut transit time and reduced drug absorption so some medications may need a corresponding increase in dose.

When the illness is short-lived and relatively minor, changes in physiology and pharmacokinetics are unlikely to be a problem for most medicines and in most patients. However, there are exceptions when patient advice about dose adjustment and monitoring for adverse outcomes may be necessary.

Important comorbidities

Patients with chronic kidney disease may be at particular risk of problems during intercurrent illness. Conditions that induce hypovolaemia increase the risk of acute kidney injury in those with reduced renal homeostatic reserve. This is potentially compounded by drugs that compromise renal homeostasis, such as renin–angiotensin system inhibitors (ACE inhibitors and sartans).

A UK position statement[1] guides the management of sick days in patients at risk of acute kidney injury, particularly when there is disturbed fluid balance. It advises patients not to use renin–angiotensin system inhibitors, diuretics, non-steroidal anti-inflammatory drugs, metformin or renally excreted sulfonylureas (e.g. glibenclamide and glimepiride) when they have vomiting or diarrhoea (unless mild), or fevers, sweats and rigors.

Other comorbidities that may impede a normal homeostatic response to disturbed fluid balance are diabetes and congestive cardiac failure. In addition, the normal homeostatic hormone responses to stress can affect glycaemic control in diabetes. In

patients with corticosteroid-induced suppression of the hypothalamic–pituitary–adrenal axis or adrenal insufficiency, the hormone response to stress may be impaired.

Controlled-release formulations

Drugs with a controlled-release formulation may be more susceptible to decreased bioavailability in severe diarrhoea.[2] For some medicines, this can be associated with a withdrawal or discontinuation syndrome (see Table),[3,4] which is predictable and potentially avoidable. This is a particular concern with shorter acting drugs in a controlled-release formulation (which depends on normal gut transit time) when the decrease in plasma concentration reduces the patient's functional status (e.g. controlled-release formulations of opioids or dopamine agonists).

Renin–angiotensin system inhibitors

When blood volume is reduced, an increase in angiotensin II promotes proximal tubule sodium reabsorption, aldosterone synthesis and thirst which act together to defend renal perfusion and the glomerular filtration rate. Illnesses that cause hypovolaemia can reduce renal perfusion. Since the normal physiological response to hypovolaemia is impaired by ACE inhibitors and sartans, patients taking these drugs are at increased risk of acute kidney injury.

When preparing its guidelines, the UK National Institute for Health and Care Excellence found no relevant publications on withholding renin–angiotensin system inhibitors during intercurrent illness. However, it concluded that the risk of acute kidney injury with their continued use outweighs the potential risk of cardiovascular events if they are temporarily stopped.[5] The guidelines suggested that patients should be advised to suspend renin–angiotensin system inhibitors during episodes of diarrhoea, vomiting and hypotension, or major infection, until they are 'clearly improving'.[5]

The Kidney Disease Improving Global Outcomes guideline recommends monitoring renal function and serum potassium in patients taking a renin–angiotensin system inhibitor during an illness that risks dehydration.[6] Given the current uncertainty, it seems reasonable to withhold these drugs in the unwell patient.

While this recommendation may sound rational, the data supporting withholding of renin–angiotensin system inhibitors in other circumstances are conflicting. In a meta-analysis of observational studies in patients undergoing surgery, when there are likely to be associated changes in haemodynamics, renin–angiotensin system inhibitors increased the odds of postoperative acute kidney injury and mortality.[7] However, a randomised controlled trial (in patients with normal baseline creatinine)[8] and a meta-analysis suggested renin–angiotensin system inhibitors were protective.[9] The more widely used renin–angiotensin system inhibitors have a reasonably prolonged half-life so a rapid offset of effect will not occur when the medicine is withheld for a few days.

The benefits from renin–angiotensin system inhibitors reflect cardiac and vascular remodelling that follows treatment over many years. Also, severe rebound hypertension does not occur following cessation of renin–angiotensin system inhibitors. Until more data are available, it is reasonable to withhold renin–angiotensin system inhibitors in patients with intercurrent illnesses associated with volume depletion until symptoms resolve.

Diuretics

Diuretics promote volume loss, which can induce renal dysfunction and change electrolytes. This may be exacerbated in patients with intercurrent illnesses. A retrospective study of older patients prescribed spironolactone in combination with an ACE inhibitor for cardiac failure found that intercurrent illness increased the risk of severe renal insufficiency and hyperkalaemia. The study recommended that spironolactone may need to be temporarily stopped during illness involving dehydration.[10] In patients at risk of dehydration or hypotension, spironolactone and probably other diuretics should be temporarily withheld.

Centrally acting antihypertensives

Most antihypertensives are not associated with marked rebound hypertension or other complications (with several important exceptions) due to a transient sub-therapeutic concentration from reduced absorption, or if discontinued.

Clonidine is an agonist at alpha$_2$ and imidazoline receptors while moxonidine predominantly acts on the I_1 imidazoline receptor.[11] Both reduce blood pressure by reducing sympathetic tone. Abrupt discontinuation of clonidine is associated with rebound hypertension higher than pre-treatment pressures.[12] This risk may be less with moxonidine.[13,14]

Rebound hypertension may be more marked if the patient is concurrently taking a beta blocker due to unopposed stimulation of alpha receptors.[15] We do not advise routinely withholding clonidine or moxonidine on sick days, but blood pressure should be monitored when drug bioavailability may be reduced.

Table **Drugs associated with adverse events in intercurrent illness**

Drug class	Drug examples	Problems arising from intercurrent illness	Potential adverse outcome
Analgesics	Hydromorphone, morphine, oxycodone, tramadol	Reduced absorption of controlled-release formulations, or deliberate cessation	Exacerbation of pain Opioid withdrawal syndrome – dysphoria, restlessness, salivation, nausea, abdominal pain and diarrhoea
	Morphine, hydromorphone	Reduced clearance in renal dysfunction, with risk of accumulation and toxicity	Opioid toxicity
Antidepressants	Venlafaxine, desvenlafaxine	Reduced absorption of controlled-release formulations, or deliberate cessation	Withdrawal syndrome – agitation, anxiety, diarrhoea, fasciculations, sensory disturbance (including shock-like syndrome, tremor, vertigo and vomiting)
Antihypertensives	Controlled-release metoprolol	Reduced absorption or deliberate cessation	Exacerbation of angina Conflicting data on association with rebound hypertension, arrhythmias[3]
	Renin–angiotensin inhibitors	Impaired physiological homeostasis, impairing renal perfusion	Acute kidney injury and hyperkalaemia
	Diuretics	Exacerbation of hypovolaemia and altered electrolyte excretion	Dehydration and electrolyte disequilibria
	Clonidine or moxonidine	Reduced absorption or deliberate cessation leading to withdrawal of central inhibitory effect	Tachycardia and hypertension
Drugs for parkinsonism	Levodopa with carbidopa or benserazide	Reduced absorption of controlled-release formulations, or deliberate cessation	Decline in motor function Case reports of neuroleptic malignant syndrome with acute withdrawal[4] featuring fever, altered mental state, rhabdomyolysis, rigidity
Mood stabiliser	Lithium	Reduced clearance in renal dysfunction with risk of accumulation and toxicity	Lithium toxicity – nausea, confusion, muscle weakness, apathy, hyperreflexia, myoclonic jerks, dysarthria, seizures
Anticoagulants	Warfarin, rivaroxaban, apixaban, dabigatran	Reduced absorption or deliberate cessation	Reduced anticoagulant effect and elevated risk of thrombosis
	Dabigatran, rivaroxaban, apixiban	Risk of accumulation in renal dysfunction	Increased anticoagulant activity leading to bleeding complications
	Warfarin	Decreased oral intake contributing to vitamin K deficiency	Increased anticoagulant activity leading to bleeding complications
	Warfarin, rivaroxaban, apixaban	Concomitant administration of anti-infectives that reduce drug clearance e.g. erythromycin (warfarin, rivaroxaban, apixaban), ciprofloxacin (warfarin) or fluconazole (warfarin)	Increased anticoagulant activity leading to bleeding complications
Antiarrhythmics	Disopyramide, flecainide, sotalol, digoxin	Reduced absorption or deliberate cessation	Reduced antiarrhythmic activity and potentially life-threatening arrhythmias
	Sotalol, digoxin	Reduced clearance in renal dysfunction	Bradycardia (sotalol and digoxin) and hyperkalaemia (digoxin)
Antiepileptics	Carbamazepine, valproate, phenytoin, levetiracetam, topiramate	Reduced absorption or deliberate cessation	Reduction in serum concentration and increased seizure risk

Table **Drugs associated with adverse events in intercurrent illness (continued)**

Drug class	Drug examples	Problems arising from intercurrent illness	Potential adverse outcome
Drugs for diabetes	Sodium-glucose co-transporter 2 inhibitors	Exacerbation of hypovolaemia and electrolyte loss	Dehydration and electrolyte disequilibria
	Metformin	Reduced clearance in renal dysfunction causing accumulation and toxicity	Nausea, anorexia, lactic acidosis
	Insulin, sulfonylureas	Inappropriate dose relative to intake and hormonal counterregulatory response (insulin and sulfonylureas) or reduced clearance in renal dysfunction causing accumulation and toxicity (glibenclamide, glimepiride)	Hypoglycaemia or hyperglycaemia
Oral contraceptives	Oestrogen and progestogen combinations	Reduced absorption or deliberate cessation	Contraceptive failure

Beta blockers

Sudden discontinuation of beta blockers can cause rebound hypertension. Acute coronary syndrome has also been reported, even in patients without coronary artery disease.[16,17] The risk of these events appears to be inversely related to the drug's half-life and the extent of receptor downregulation.[18]

Drugs for diabetes

Patients able to self-manage their diabetes medicines should be provided with a management plan for use during sick days. Patients who are not monitoring their own glucose should be advised to see their doctor when becoming ill.

Insulin

During intercurrent illness, there is generally an increased insulin requirement due to upregulation of counter-regulatory hormones, particularly cortisol, so temporary changes to the insulin dose may be required. Despite a reduced nutritional intake, insulin should not be routinely withheld in type 1 or 2 diabetes.

For type 1 diabetes, guidelines suggest that patients administer supplemental doses of short-acting insulin every 2–4 hours if blood glucose remains elevated. If there is no improvement in either blood glucose or blood ketones after two extra supplemental doses of insulin, medical review should be sought.[19] Patients should increase the frequency of blood glucose monitoring and add regular blood ketone measurements if their glucometer allows.

In type 2 diabetes, patients should increase blood glucose monitoring to 3–4 times daily during acute illness. If readings are persistently above 15 mmol/L then the morning dose of long- or intermediate-acting insulin may need to be increased by 10–20%.[20] For those taking short-acting insulin, the dose will need to be adjusted based on the results of their blood glucose readings and dietary carbohydrate intake.

Metformin

Patients should withhold metformin during significant illness to reduce the risk of lactic acidosis. Although more strongly associated with its predecessor phenformin, cases of lactic acidosis have also been reported with metformin.[21] Observational studies suggest that it may be more common during intercurrent illness, particularly when there is vomiting, diarrhoea and acute kidney injury.[22] Metformin is unlikely to induce hypoglycaemia but it can aggravate symptoms of nausea, vomiting and diarrhoea, which may increase the risk of renal dysfunction. Vomiting and diarrhoea can be early signs of lactic acidosis and may prompt further investigation.[22]

Sulfonylureas

Patients with severe intercurrent illness generally have an increase in blood glucose. The use of sulfonylureas may limit hyperglycaemia and the risk of a hyperosmolar syndrome. However, patients can experience reduced blood glucose in some instances, such as when severe anorexia and gastroenteritis compromise caloric intake. Patients using sulfonylureas should be advised about the increased risk of hypoglycaemia and should have a low threshold for ceasing their sulfonylurea and seeking medical assessment should they develop low blood glucose readings. Those taking sulfonylureas or repaglinide should continue their treatment and increase blood glucose monitoring to at least twice daily (before meals, including before breakfast). This needs to be done with additional caution for glibenclamide and glimepiride, which have renally excreted active metabolites,[23,24] and may require closer monitoring of blood glucose.

Glucagon-like peptide-1 analogues and dipeptidyl peptidase-4 inhibitors

While glucagon-like peptide-1 analogues have gastrointestinal adverse effects, they are considered safe in acute illness as they are not associated with hypoglycaemia[25] or complications such as lactic acidosis or renal failure.[26] This is because they stimulate insulin release via a glucose-dependent mechanism.

The dipeptidyl peptidase-4 inhibitors (DPP-4 or gliptins) are also considered safe. They potentiate the effect of endogenous glucagon-like peptide-1 by inhibiting its metabolism.

In patients taking either of these drug classes, acute abdominal pain as part of an intercurrent illness should prompt assessment for possible drug-induced pancreatitis.[19]

Sodium-glucose co-transporter 2 inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors have an osmotic diuretic effect and should be withheld due to the risk of worsening dehydration. They have also been associated with euglycaemic ketoacidosis and therefore may contribute to the development of diabetic ketoacidosis.

Corticosteroids

The hypothalamic–pituitary–adrenal axis is suppressed in patients taking corticosteroids (≥prednisolone 5 mg/day or equivalent), and the normal response to severe illness is blunted. Corticosteroid doses need to be increased to mimic the normal physiological response to prevent haemodynamic instability from a relative hypoadrenal state. For example, methods for steroid escalation in acute illness include:

- increase the dose to an equivalent of hydrocortisone 50–75 mg/day (or prednisolone 12.5–20 mg/day)[27]
- double the dose for two days before returning to the patients' usual dose when they feel better.[28]

If oral therapy is compromised by severe diarrhoea or vomiting, parenteral hydrocortisone may be necessary.[28] Mineralocorticoids do not need to be adjusted.

Digoxin

Vomiting and diarrhoea can contribute to digoxin toxicity by two mechanisms. First, gastroenteritis can result in hypokalaemia, which potentiates the effect of digoxin. Second, the reduced glomerular filtration rate associated with hypovolaemia reduces digoxin clearance. Digoxin toxicity can manifest as nausea and vomiting, which can further exacerbate hypovolaemia and hypokalaemia.

Given that digoxin has a prolonged half-life with normal renal function, it is safe and probably reasonable to withhold digoxin for 1–2 days in severe gastroenteritis. While the stated therapeutic reference range is 0.6–2.6 nmol/L, the current recommendation is to use lower doses and aim for a lower target concentration in the therapeutic range.[29] The risk of toxicity from ongoing dosing is probably low in short-lived gastroenteritis.

Oral contraception

The loss of efficacy of the oral contraceptive pill (combined and progestogen-only) has been reported with diarrhoea and presumably relates to impaired absorption and sub-therapeutic hormone levels. Guidance for managing missed pills is applicable to intercurrent illness.

Combined oral contraceptive pill

If only one dose has been affected by the illness, the pill should be taken when symptoms stop and then the rest of the pack continued as usual. Two doses may need to be taken on the same day. No additional contraception is required.[29]

If the illness lasts for two or more pill-taking days, contraception will be affected. The last missed pill should be taken at the end of the illness and then the rest of the pack should be taken as usual. Barrier contraception is required for the next seven days. Active pills need to be taken for the next seven days after the illness to ensure contraception. This may require skipping the pill-free period and commencing the active pills of the next pack.[29]

Progestogen-only pill

If illness lasts longer than three hours, contraceptive efficacy will be affected and the next pill should be taken as soon as the illness concludes (this may mean taking two pills on the same day). Barrier contraception should be used for the next two days.[30]

Other drugs

There are many other drug classes where interruptions to therapy can have adverse therapeutic consequences (see Table). Continuing these medicines with an unchanged dosing regimen during a brief episode of acute illness is unlikely to predispose patients to adverse events. In a patient whose symptoms are persistent or severe enough to either cause a significant electrolyte derangement or acute kidney injury, early assessment of serum electrolytes and renal function may allow early detection and intervention.

People on chronic antimicrobial therapy such as antiretrovirals for HIV should continue these if possible. This reduces the risk of losing control of the infection and the potential emergence of antimicrobial resistance.

Conclusion

Acute illness can result in significant changes to drug pharmacokinetics, which can either cause adverse drug events or potentiate the illness. In relatively healthy individuals, alterations in pharmacokinetics are usually transient and not clinically significant. However, some patients are at risk of a serious adverse event so it is important to identify them based on their medication regimen and comorbidities. Understanding the principles of pharmacokinetics and potential complications should help clinicians provide better information to patients and more comprehensive 'sick day' plans. This may improve long-term adherence and chronic disease management. ≺

Darren Roberts is the Chair of the Editorial Executive Committee of Australian Prescriber.

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ARTICLE

Prescribing for frail older people

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SUMMARY

Frailty is associated with greater exposure to polypharmacy and medicines with anticholinergic and sedative effects, which may increase the risk of adverse outcomes including falls.

People who are frail experience a higher incidence and severity of adverse drug events because of their medicine use and potential changes in pharmacokinetics and pharmacodynamics.

Prescribing for these patients requires constant vigilance and review, considering the impact of every medicine, as well as overall drug load, comorbidities, function and goals of care.

Introduction

Frailty is a multifactorial syndrome associated with functional impairment and increased susceptibility to disease, disability and mortality and can occur at any age. The clinical definition describes frailty as 'a state of vulnerability to poor resolution of homeostasis following a stress and is a consequence of cumulative decline in multiple physiological systems over a lifespan'.[1]

Although at present, there is no universal way to identify patients with frailty in clinical practice, the two most common approaches used in research are:[1]

- the phenotype model – frailty defined as the presence of at least three criteria including exhaustion, weakness, unintentional weight loss, slow walking, low physical activity
- frailty indices – accumulation of medical, functional or social deficits.

The prevalence of frailty defined using the phenotype criteria is 9.9% across studies conducted in community-dwelling older adults. Frailty increases with age – 15.7% of adults aged 80–84 years were identified as frail compared with 26.1% of those aged 85 years and over.[2] Frailty is very common in Australian acute geriatric medicine inpatients (approximately 90%)[3] and in residents of aged-care facilities (approximately 40%, depending on country studied and scale used).[4] Frailty is a dynamic state and people can move in and out of it.

Medicine use in frail people

There is a lack of guidelines to inform appropriate prescribing for frail older adults. They tend to receive more drugs than robust older adults. In community-dwelling older men, polypharmacy (≥5 drugs) was reported in 64.7% of frail men compared with 27.2% of robust men.[5] Using the Drug Burden Index, which is associated with functional impairment in older people, exposure to anticholinergic and sedative medicines was reported in 45.5% of frail men compared with 20.1% of robust men. Preventative drugs such as statins are used less often by frail men than by robust men (7.6% vs 10.4%).[6]

In acute care, frail patients use significantly more medicines overall compared with other patients (frail 9.8 ± 4.3 vs robust 4.4 ± 3.3), and more medicines that increase the risk of falls (frail 3.4 ± 2.2 vs robust 1.6 ± 1.5).[7] This was also observed in a national sample of inpatients, with higher frailty indices seen in patients with polypharmacy and hyperpolypharmacy (≥10 drugs).[8]

Impact of frailty on pharmacokinetics and pharmacodynamics

Evidence of the impact of frailty on drug disposition and effects is very limited. Animal models of frailty are only just starting to emerge, which may shed some light on the impact of frailty on pharmacokinetics and pharmacodynamics.[9]

Applying the limited evidence on the clinical pharmacology of frailty is challenged by different definitions of frailty in trials. For example, many studies use living in a nursing home as a frailty surrogate, although not all nursing home residents are frail when measured by objective measures. Also, studies are often underpowered because of the difficulty recruiting and sampling from frail older people and because this population has increased inter-individual variability.

The physiological changes of frailty are likely to impact on pharmacokinetics and pharmacodynamics. These are outlined in Table 1, along with any evidence available.[7,10-17]

Table 1 **Impact of frailty on pharmacokinetics and pharmacodynamics**

Pharmacology	Physiological changes with frailty	Hypothesised impact of frailty	Data comparing frail and robust older people
Absorption	Slowed gastric motility and reduced hepatic metabolism	Delayed absorption and reduced bioavailability of drugs administered orally	–
Distribution	Sarcopenia and relative adiposity	Reduced volume of distribution of water-soluble drugs and increased volume of distribution of fat-soluble drugs	Volume of distribution of gentamicin not significantly reduced in frailty* [10]
	Reduced plasma albumin	Decreased protein binding of acidic drugs	
Metabolism	Reduced hepatic volume and blood flow	No consistent effects on phase I clearance	No independent effect of frailty on erythromycin breath test (measures CYP3A4 and P-glycoprotein)* [11]
		Reduced phase II clearance	Aspirin esterase activity reduced in plasma [12] but not in liver in frailty [13]
			Reduced paracetamol clearance in frailty [14]
Excretion	Glomerular filtration rate reduced	Reduced renal drug clearance	Reduced gentamicin clearance in frailty* [10,15]
Pharmacodynamics	Reduced resilience to external stressors	Exaggerated or reduced drug effects	Increased sedation with metoclopramide [16]
	May be some reduced receptor function in presence of chronic inflammation		Increased susceptibility to falls with drugs acting on the CNS and cardiovascular system* [7]
			May be reduced response of platelet aggregation to aspirin in frailty* [17]

* Study used an objective measure of frailty. CYP cytochrome P450 CNS central nervous system

Increased risk of adverse effects

People who are frail are more likely to experience adverse drug events because of their patterns of drug use and, potentially, changes in pharmacokinetics and pharmacodynamics. Also they are more susceptible to the effects of adverse drug reactions because of reduced resilience. Patients with a higher frailty index score are twice as likely to have at least one potentially inappropriate medicine prescribed. They are also more likely to experience an adverse drug reaction compared to those below the frailty threshold.[18]

Recent evidence suggests that increasing medication load is associated with transitioning from the pre-frail to frail status and subsequent death. Each additional drug was associated with a 22% greater risk of death in men who were initially defined as robust.[19] Pharmacoepidemiological studies on the effects of specific drug classes, such as ACE inhibitors[20] or statins,[21] on incident frailty have not found significant associations.

Results from clinical trials

Trial results observed in the general population cannot necessarily be extrapolated to the frail population. Studies of the impact of frailty on the effects of medicines show varying results (see Table 2).[6-8,22-25] The observational studies highlight the effects of polypharmacy, the use of drugs that increase the risk of falls, and drugs recommended by guidelines for secondary prevention of cardiovascular disease. They suggest that frail older people are more susceptible than non-frail to adverse outcomes, such as falls, institutionalisation and death with drug use.

There are also secondary analyses of randomised controlled trials that examine the impact of frailty on different treatment outcomes. These suggest that with antihypertensive treatment, frail participants may get similar reductions in cardiovascular outcomes and mortality compared to non-frail participants.

Recent debate has focused on whether frailty should be considered when prescribing antihypertensives to older adults. The Hypertension in the Very Elderly Trial (HYVET) suggests benefit with antihypertensive therapy irrespective of frailty status.[25] In the Systolic Blood Pressure Intervention Trial (SPRINT) of adults aged 75 years or older, treating to a systolic blood pressure target of less than 120 mmHg compared with a target of less than 140 mmHg resulted in significantly lower rates of fatal and nonfatal major cardiovascular events and all-cause mortality.[24] Frailty did not appear to modify this relationship, although the trial was not powered to assess this.

Table 2 **Medication outcomes in older people stratified by frailty status**

Study	Participants (number, mean age)	Frailty definition	Outcomes
Peeters et al. 2016* [22]	Community-dwelling women with ischaemic heart disease and using at least one guideline-recommended drug (n=885, 82.7 years)	'Frail scale' i.e. at least 3 of • >5% weight loss over 3 years • feeling fatigued • difficulty climbing stairs • difficulty walking 100 m • having ≥5 chronic conditions	Adherence to optimal therapy associated with increased risk of falls with no significant gain in cardiovascular health
Gnjidic et al. 2015* [23]	Community-dwelling men with ischaemic heart disease (n=462, 78 years)	Presence of geriatric syndromes including frailty (defined using modified frailty phenotype)	Optimal therapy associated with lower risk of institutionalisation and mortality, stratified according to presence of geriatric syndromes including frailty
Gnjidic et al. 2013* [6]	Community-dwelling men (n=1665, 76.9 years)	Modified frailty phenotype	Frail men more likely to be institutionalised or die than robust men, regardless of their statin use
Poudel et al. 2016* [8]	Inpatients (n=1418, 81 years)	Frailty index	Risk of composite adverse outcome higher in frail patients with polypharmacy compared to robust patients with polypharmacy
Bennett et al. 2014* [7]	Inpatients admitted with falls (n=204, 80.5 years)	Reported Edmonton frail scale	Risk of recurrent falls increased in frail patients taking 1.5 FRIDs and in robust patients taking 2.5 FRIDs
Williamson et al. 2016 (SPRINT trial)† [24]	Community-dwelling adults with hypertension and without diabetes (n=2510, 79.9 years)	Frailty index	Effects of intensive vs standard blood pressure treatment not significantly modified by frailty status
Warwick et al. 2015 (HYVET trial)† [25]	Community-dwelling adults with hypertension (n=2656, indapamide ± perindopril group: 83.6 ± 3.2 years, placebo group: 83.4 years)	Frailty index	Antihypertensive treatment reduced risk of stroke, all-cause mortality or cardiovascular events in both frail and robust patients

* observational study
† clinical trial
FRIDs falls-risk increasing drugs, refers to all drugs acting on the central nervous system or cardiovascular system (e.g. sleeping pills)
SPRINT Systolic Blood Pressure Intervention Trial
HYVET Hypertension in the Very Elderly Trial

Drug interactions

The prevalence of clinically relevant drug–drug interactions is higher in frail compared to robust inpatients. Our studies in a tertiary referral hospital identified more potential interactions in frail patients compared to robust patients (35% vs 5%).[7] Clinically relevant statin interactions were found in 9.5% of frail versus 6.8% of robust older inpatients.[26]

Deprescribing

Deprescribing is defined as withdrawing an inappropriate medicine, supervised by a healthcare professional, with the goal of managing polypharmacy and improving outcomes.[27,28]

In view of the limited evidence of benefit for medicines in frail older people and strong observational evidence of the increased risk of and from adverse drug events, trials of deprescribing have recently been conducted in frail older people. In a Western Australian study of people living in residential aged-care facilities, individualised medication reviews significantly reduced the number of regular medications by 2.0 ± 0.9 (95% confidence interval 0.08–3.8, p=0.04) compared to the control group, with no significant change in clinical outcomes.[29]

Irish consensus criteria on drugs that are potentially inappropriate in frail older patients with limited life expectancy have recently been published.[30]

Known as 'STOPPFrail' (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy), they suggest deprescribing any medicine without a clear clinical indication or where compliance is poor, and include specific recommendations for 25 drug classes and indications.

Tailoring therapy for frail older people

When prescribing for older people, frailty status should be considered when applying the six steps in the World Health Organization's Guide to Good Prescribing.[31] Medicines prescribed for chronic conditions need to be reviewed frequently to assess whether they are providing net benefit or net harm. Goals of care change frequently in frail people, and changes should prompt and inform re-evaluation of the patient's prescriptions. Opportunities to re-evaluate goals and treatment with patients and their families include acute admission to hospital, admission to a residential aged-care facility, and functional decline or a terminal illness such as the terminal phase of dementia.

Step 1: Define the patient's problem

Diagnoses can be difficult in frail older people as they often present with non-specific multifactorial geriatric syndromes such as falls, cognitive impairment and incontinence. Their presentation may also be affected by a reduced response to external stressors, for example they may not develop a fever or increased white cell count in response to an infection. Frailty may also impact on clinical decisions to conduct investigations. It is important to consider whether the patient's presentation is attributable to an adverse drug event as these are the most reversible causes of the geriatric syndromes. Also failure to recognise an adverse drug event could inadvertently result in a prescribing cascade.[32]

Step 2: Specify the therapeutic objective

The therapeutic objective refers to the desired pharmacodynamic effect of the drug. Frail older people are rarely represented in clinical trials, so there is limited evidence to support the efficacy and safety of most treatments for these patients. Often observational data or secondary analysis of clinical trial data can be used to inform therapeutic decisions (see Table 2). For example, in secondary prevention of cardiovascular disease, observational data suggest that optimal medical therapy (aspirin, ACE inhibitor, beta blocker and statin) reduce the risks of institutionalisation and mortality to a similar extent in older men with and without geriatric syndromes including frailty.[23] There is also increasing evidence from subgroup analyses on the impact of polypharmacy on the safety and efficacy of drugs for specific disease states.[33]

Step 3: Verify whether the treatment is suitable for the patient

In people with multiple morbidities and disability, the benefit of the drug must be considered in view of the patient's other conditions, other medicines (and potential drug interactions) and global therapeutic objectives (goals of care). A full medication review is essential before starting a new medicine. For example, subgroup analysis of controlled trial data suggests that in frail older people intensive blood pressure control may reduce the risk of cardiovascular events, stroke and mortality.[25] However, these outcomes may not be as high a priority for some frail older patients as reducing the risk of falls, which may increase with antihypertensives.

Step 4: Start the treatment

Discuss the therapeutic decision with the patient and their carers. Adjust the dose to account for the pharmacokinetic and pharmacodynamic changes of frailty (see Table 1). Use formulations that make administration simple. For example, use once-daily slow-release formulations if the patient can swallow them.

Step 5: Provide information, instructions and warnings

It is important to give clear information verbally and in written form to the patient, their carers and other healthcare providers, including any specialists. An updated medication list is also important. Follow-up is important to ensure that the patient's plan has been communicated and is being implemented. Warnings should include adverse events seen commonly in frail older people that may not be prominent on standard consumer medicine information, such as the risks of falls, confusion, incontinence and polypharmacy.

Step 6: Monitor (stop) the treatment

Treatment can be stopped when the problem has been solved. In frail older people, 'solving' acute problems with medicines may involve completing a course of antimicrobials for an infection or analgesics for acute pain. If treatment for an acute or chronic problem is not effective, safe or convenient, it needs to be reviewed using the six steps again.

If a decision is made to stop a medicine, it is important to check whether it can be stopped suddenly or needs to be weaned gradually.[34] It is important to monitor the outcomes of stopping treatment. These may include adverse drug withdrawal events, but more often than not there is no change or any adverse effects resolve quickly.

Conclusion

Frail older people are major users of medicines, despite a paucity of evidence on pharmacokinetics and pharmacodynamics and decreased resilience to adverse drug events in this population. When prescribing it is essential to consider the patient's goals of care, function, comorbidities and overall medication load. Frequently review all medicines for frail older patients to ensure that they are receiving net benefit. Clinical trials (including deprescribing trials) and observational studies are starting to include objective measures of participants' frailty. This will help prescribers assess how the findings apply to frail and robust older patients in clinical practice. ≺

Conflict of interest: none declared

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ARTICLE

Treatment of fibromyalgia

SUMMARY

Fibromyalgia is a common, often overlooked, clinical syndrome in general practice. It can be associated with considerable disability, but this is likely to be minimised by early diagnosis and intervention.

Patients with fibromyalgia often have other chronic conditions. Careful clinical evaluation and management of aggravating factors can therefore be beneficial.

A coordinated, patient-centred, multidisciplinary approach to management is required. Patients need education and strategies for self-management of their condition. Non-drug interventions such as physical therapy should be tailored to the individual patient.

Active rehabilitative approaches have primacy in management, but drugs can help to control symptoms. There is evidence to support the use of amitriptyline, duloxetine, milnacipran or pregabalin, but pure opioids should be avoided.

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Keywords
amitriptyline, duloxetine, fibromyalgia, milnacipran, pregabalin

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Introduction

Fibromyalgia is a debilitating and often unrecognised syndrome. It affects 2% of the population with a peak incidence in middle-aged women.[1] Despite an incomplete understanding of its pathogenesis, there is increasing evidence for mechanism-based management approaches to this syndrome.[2,3] These are likely to be more effective if introduced early, making timely diagnosis in general practice even more important.

Fibromyalgia overlaps with other functional somatic syndromes, such as irritable bowel syndrome, chronic fatigue syndrome and temporomandibular joint dysfunction.[4] While commonly co-occurring with mood and anxiety disorders, research suggests that, although functional somatic disorders are related and potentially interact with psychological conditions, they are independent.[5]

The syndrome is characterised by its hallmark features of widespread somatic pain and deep tissue tenderness, which result from sensitisation of neural pain pathways.[6] There are also variable combinations of fatigue, sleep disturbance, cognitive dysfunction and psychological distress. These symptoms occur despite the absence of objective abnormalities on clinical assessment.

Pathophysiology

Fibromyalgia can develop spontaneously,[7] but is likely to represent a stereotypical, maladaptive, biological response of the body to the cumulative effects of physical or psychological stress in genetically predisposed people.[8] It is associated with psychiatric and musculoskeletal disorders, leading to poorer outcomes,[9,10] but it also can occur after an infection. Furthermore, fibromyalgia may occur with increased prevalence in people with chronic medical disorders in general.[11]

Although fibromyalgia has been considered to primarily derive from pathophysiology within the central nervous system, where it is associated with disordered sensory processing, there is growing evidence to suggest that the 'fibromyalgia phenotype' may comprise multiple pathogenetic subsets, including originating, at least in part, within the peripheral nervous system.[6,12,13] Most cases of fibromyalgia evolve out of persistent regional pain.[14]

Diagnosis

Diagnostic criteria[15] have evolved from a recognition that fibromyalgia is a spectrum disorder, both with regards to spatial distribution of pain and symptom involvement and severity. This spectrum has been described as 'fibromyalgianess', and not as a discrete all-or-none disorder, as suggested by the original classification criteria.[16]

Given the multidimensional nature of fibromyalgia, including its association with other chronic medical disorders, clinical assessment in time-poor general practice can be challenging. The condition should be considered as a diagnostic possibility in all cases of persistent, significant musculoskeletal pain, fatigue or sleep disturbance, particularly when such symptoms seem out of proportion to the severity of any background chronic illness.[17] If any diagnostic doubt exists, referral to a rheumatologist or pain medicine specialist can be considered.

A validated, practical, self-assessment tool based on the diagnostic criteria has been developed (Box 1)[18] to quantitate the protean symptoms of the syndrome.[19,20] Scores above certain thresholds[20] yield reasonable specificity and sensitivity compared to the original classification criteria,[16] providing assessment by the diagnosing clinician excludes other disorders that fully explain the symptoms.[21] Examination for deep tissue tenderness, which was required by the old criteria, is now avoided. Investigations are only needed to exclude treatable comorbidities and potential differential diagnoses, such as thyroid dysfunction.[22]

Management

Spontaneous recovery is unusual so the aims of management are to improve symptoms, function and the quality of life.[23] There are several steps in the treatment pathway and these should be individually tailored. Treatment is multimodal, multidisciplinary and combines non-pharmacological and pharmacological approaches.[2]

Although the effect sizes for interventions in fibromyalgia are generally small, these are average measures. There are subgroups of patients who will have significant benefits from particular therapeutic approaches.[3,24] The effect sizes for non-pharmacological approaches tend to be larger than those for drugs, but combinations of drugs have only recently started to be tested. There have been some positive results,[25-27] emphasising the potential utility of a multimodal approach.

Treatment of aggravating disorders

The pain sensitisation experienced by patients with fibromyalgia is thought to result from the integrated effects of disturbed ascending facilitatory and

Box 1 **Fibromyalgia survey questionnaire**

I. Using the following scale, indicate for each item the level of severity over the past week by checking the appropriate box.

0: No problem
1: Slight or mild problems; generally mild or intermittent
2: Moderate; considerable problems; often present and/or at a moderate level
3: Severe; continuous, life-disturbing problems

Fatigue	☐ 0	☐ 1	☐ 2	☐ 3
Trouble thinking or remembering	☐ 0	☐ 1	☐ 2	☐ 3
Waking up tired (unrefreshed)	☐ 0	☐ 1	☐ 2	☐ 3

II. During the past 6 months have you had any of the following symptoms?

Pain or cramps in lower abdomen	☐ Yes	☐ No
Depression	☐ Yes	☐ No
Headache	☐ Yes	☐ No

III. Joint/body pain

Please indicate below if you have had pain or tenderness over the past 7 days in each of the areas listed below. Please make an X in the box if you have had pain or tenderness. Be sure to mark both right side and left side separately.

☐ Shoulder, left	☐ Upper leg, left	☐ Lower back
☐ Shoulder, right	☐ Upper leg, right	☐ Upper back
☐ Hip, left	☐ Lower leg, left	☐ Neck
☐ Hip, right	☐ Lower leg, right	
☐ Upper arm, left	☐ Jaw, left	☐ No pain in any of these areas
☐ Upper arm, right	☐ Jaw, right	
☐ Lower arm, left	☐ Chest	
☐ Lower arm, right	☐ Abdomen	

IV. Overall, were the symptoms listed in I–III above generally present for at **least 3 months**? ☐ Yes ☐ No

Source: Reference 18

descending inhibitory influences, potentially at multiple levels in the central nervous system. There therefore needs to be careful clinical evaluation and management of disorders which can aggravate this disturbed neurophysiological balance (see Box 2).

Non-pharmacological approaches

The burden of living with fibromyalgia is higher than with other rheumatic disorders and higher than with most other chronic illnesses.[1,9,10,28] As the medical management of fibromyalgia is often only partially successful,[2] health professionals need to give patients sustained support to become expert, active self-managers. This is the most important of all interventions to enable successful living with this debilitating multidimensional disorder. However, cognitive dysfunction related to the fibromyalgia, which is often not recognised by treating professionals, can make this process challenging.

Growing evidence suggests self-management skills training is best delivered within a supportive small group setting where education, coping skills training, and cognitive behavioural approaches can be explored.[29] Skills thereafter can perhaps be consolidated by trained peer mentors.[30] In Australia effective and sustainable models of care are yet to be developed, although internet and generic chronic pain courses can be used.[31,32] For all health professionals, an open and patient-centred communication style is strongly recommended.[33]

In general, exercise and psychoeducational approaches have the greatest evidence of efficacy among non-pharmacological therapies,[2] but they need to be tailored to the individual. Pre-exercise biomechanical assessment and subsequent exercise monitoring by a knowledgeable physical therapist are desirable for all but the mildest cases. Promotion of daily physical activity can be assisted by use of an actimeter.[34] Referral to a psychologist should be considered in all patients, particularly those who are more psychologically distressed.

Pharmacological approaches

Some patients either do not tolerate or benefit from drugs. Drug therapy only has a supportive role in symptom management. All drugs should be started at low doses and cautiously increased. They should be chosen to manage the individual's predominant symptoms, with pain, sleep disturbance and psychological distress being the most amenable to drug therapy. Stop the drug if it provides no benefit.

Antidepressants

Low-dose amitriptyline has traditionally been the first-line drug for treating pain and sleep disturbance in fibromyalgia. However, the evidence supporting its use is low quality. Studies are small and short-term, but show 4.1 patients need to be treated for one to have at least 50% pain relief. However, for every 3.3 patients treated, one will have an adverse event.[35] Tolerance development and weight gain limit the use of amitriptyline, but in a small subgroup it can be very useful in the long term.

Mediators of descending inhibition in the nervous system include serotonin and noradrenaline (norepinephrine). Their concentrations are reduced in subgroups of patients with fibromyalgia, justifying a trial of a serotonin noradrenaline reuptake inhibitor.

Duloxetine at 60 mg per day has a number needed to treat for at least 50% pain relief of 8 while the number needed to harm is 18 (all neuropathic conditions pooled) in moderate-quality studies.[36] It is not approved for fibromyalgia in Australia and its benefit for other core symptoms of fibromyalgia is marginal.

Milnacipran inhibits the reuptake of serotonin and noradrenaline (norepinephrine). It has been approved in Australia for the treatment of fibromyalgia rather than depression. The recommended dose is 100 mg daily in divided doses and requires a private prescription. High-quality evidence shows it has modest efficacy. The number needed to treat for at least 30% pain relief is 11 with a number needed to harm of 14.[37] Milnacipran could have a particular role in the management of obese patients, as it appears to have no weight-promoting potential and may cause mild weight loss.[38]

Antiepileptic drugs

The concentrations of the pain facilitatory neurotransmitters glutamate and substance P in the central nervous system are elevated in fibromyalgia. They are the targets of pregabalin and gabapentin, which have potential pain modulatory, physiological-

Box 2 Factors that aggravate pain in fibromyalgia

- Persistent peripheral pain generators (spinal and/or peripheral arthritis, tendinopathies and myofascial trigger points)
- Sleep disorders (obstructive sleep apnoea, restless legs and periodic limb movement disorder)
- Obesity (with consequent pain-sensitising effects of meta-inflammation)
- Smoking
- Opioid-induced hyperalgesia
- Statin myopathy
- Depression
- Catastrophising cognitive style
- Psychosocial stressors

sleep-promoting and anxiolytic actions. High-quality evidence shows that for pregabalin the number needed to treat for at least 50% pain relief is 12 with a number needed to harm of 13. Pregabalin also has a small benefit for sleep,[39] but weight gain frequently limits its use. Although pregabalin is not listed on the Pharmaceutical Benefits Scheme (PBS) for fibromyalgia, the frequent co-occurrence of neuropathic pain meets PBS requirements.

Other drugs

There is preliminary evidence from randomised controlled trials of efficacy in subgroups treated with tramadol,[40] pramipexole[41] and memantine.[42] Pure mu-opioid receptor agonists, such as codeine, fentanyl and oxycodone, are contraindicated because of poor clinical response and increased risk of opioid-induced hyperalgesia.[40] There is no trial evidence of efficacy for paracetamol used alone and there is weak evidence that non-steroidal anti-inflammatory drugs are ineffective.[2]

Conclusion

Fibromyalgia can be associated with profound, multidimensional disability. Multidisciplinary management is needed. A systematic, patient-centred approach in general practice can yield clinically meaningful improvements in symptom control, function and quality of life of patients with this challenging disorder. Non-pharmacological treatments have an important role.

Drugs can usefully complement an active rehabilitation program. There is some evidence for amitriptyline, duloxetine, milnacipran and pregabalin, but not all patients will benefit. Patients should be monitored for adverse events as these can limit the benefits of drug treatment. ◀

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. Benzodiazepines are the first-line drugs for the sleep disorders associated with fibromyalgia

4. Pure opioids should not be used to treat fibromyalgia

Answers on page 203

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ARTICLE

Antibiotic prophylaxis for dental procedures

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SUMMARY

Patients at risk of developing infective endocarditis or infection of a prosthetic joint may require antibiotic prophylaxis during dental treatment.

Current guidelines recommend prophylaxis less often than in the past. This is because of concerns about antimicrobial resistance and an increased understanding about the daily incidence of bacteraemia.

There is international variation in the recommendations for preventing infective endocarditis so Australian health professionals should consult Australian guidelines. Conditions for which prophylaxis is still recommended include prosthetic heart valves and rheumatic heart disease in patients at high risk of endocarditis.

Most experts no longer recommend antibiotic prophylaxis for dental procedures in patients with prosthetic joints.

Introduction

Antibiotic prophylaxis has been used in dentistry for patients at risk of infective endocarditis or prosthetic joint infection. The scientific rationale for prophylaxis was to eliminate or reduce transient bacteraemia caused by invasive dental procedures. Despite a long history of use and multiple guidelines for prophylaxis, there remains uncertainty about its effectiveness. In the last 10 years, there have been significant changes to the guidelines for antibiotic prophylaxis. These changes have been driven partly by global concerns about antimicrobial resistance[1] and subsequent recommendations that any prescription of antibiotics should be appropriate and judicious.[2]

Another factor that has driven the changes has been the recognition that the incidence of transient bacteraemia caused by oral hygiene procedures is often the same as the incidence caused by many dental treatments for which prophylaxis has traditionally been given. Regular toothbrushing and flossing pose a greater risk in relation to both infective endocarditis[3] and prosthetic joint infection[4] than episodic dental treatment.

Toothbrushing,[5] flossing,[6] pulsating water irrigators[7] and interdental woodsticks[8] can all produce bacteraemia. Gingival inflammation has been significantly associated with an increased incidence of bacteraemia caused by toothbrushing.[9] However, the incidence of bacteraemia with flossing does not differ significantly between people with or without periodontal disease.[10] The incidence and magnitude of bacteraemia caused by flossing are the same as that caused by deep scaling/root planing within the same patients,[11] yet deep scaling/root planing is considered an 'invasive dental procedure' that has traditionally required antibiotic prophylaxis.

Infective endocarditis

The annual incidence of infective endocarditis is approximately 3–10 per 100 000 people[12] but its mortality rate is around 20%.[13,14] About half of all cases occur in patients with no known cardiac risk factors.[14] Staphylococci cause the majority of cases in developed countries[12,13] with the highest incidence found in patients over 65 years old undergoing diagnostic or interventional procedures in hospitals.[14]

Viridans streptococci are found as commensal organisms in the mouth and in plaque. They account for approximately 20% of native valve and 25% of cases of late prosthetic valve infective endocarditis.[15] Studies show that viridans streptococcal bacteraemia occurs commonly with invasive dental treatments, especially tooth extraction.[16] Anaerobic oral bacteria seldom cause infective endocarditis.[17]

Evolution of prophylaxis guidelines

Since the 1950s there has been a progressive reduction in the use of antibiotics in the prevention of endocarditis following dental therapy (see Table). Different countries have made different recommendations. The changes in the USA in 2007 limited prophylaxis to patients with conditions including prosthetic cardiac valves or valves repaired with prosthetic material, previous infective endocarditis, unrepaired and repaired congenital cardiac defects and cardiac transplants with subsequent valvulopathy. Patients with mitral valve

Table **Evolution of guidelines for endocarditis prophylaxis**

Year	Organisation	Recommendation for patients without penicillin hypersensitivity
1955	American Heart Association	Intramuscular benzylpenicillin for all patients at risk
1982	British Society for Antimicrobial Chemotherapy	Oral amoxicillin, 3 g one hour before treatment, 1.5 g six hours after treatment
1997	American Heart Association	Oral amoxicillin, 2 g one hour before treatment
2007	American Heart Association	Prophylaxis limited to high-risk patients
2008	National Institute for Health and Clinical Excellence (UK)	No antibiotic prophylaxis

prolapse, even with severe regurgitation, no longer required prophylaxis.[18]

In 2008 the abolition of antibiotic prophylaxis for all patients in the UK was a radical change in practice.[19] It resulted in considerable controversy including claims from UK cardiologists that patient safety would be compromised.[20] There were allegations of making a cost-effectiveness judgment on the basis of insufficient evidence and for instituting a de facto population-wide clinical trial.[21]

Following these changes in the USA and UK, revised infective endocarditis prophylaxis guidelines were soon introduced in Australia,[22] New Zealand[23] and Europe.[24] These countries followed the USA and reduced the types of cardiac conditions requiring prophylaxis.

The reason for differing opinions on prophylaxis is the lack of evidence on which to base conclusions. A Cochrane review found no randomised controlled trials that had studied the efficacy of antibiotic prophylaxis for preventing infective endocarditis due to dental treatment.[25] This review identified only one case-control study[26] which found no significant effect of penicillin prophylaxis. The review therefore concluded that there was no evidence that antibiotic prophylaxis was effective or ineffective in preventing infective endocarditis in at-risk individuals undergoing invasive dental procedures.[25]

Outcome studies

As there is a lack of evidence about the efficacy of antibiotic prophylaxis, expert groups have assessed studies investigating associations between guideline changes and the incidence of infective endocarditis. While an increased incidence following a reduced use of antibiotics would suggest that there is a need for prophylaxis, methodological limitations in some studies mean that it is difficult to say that the cases of endocarditis were related to dental procedures.

Two retrospective studies in the USA[27,28] showed no changes in the rate of infective endocarditis due to viridans streptococci three years after the revision of the guidelines in 2007. A third study found a significant increase in streptococcal infective endocarditis, but it did not report the incidence of viridans streptococcal infective endocarditis, nor provide any data on dental treatment or antibiotic prophylaxis.[29] No firm conclusions can therefore be drawn about the impact of the change in the guidelines.

In France, a prospective study[30] found no increase in infective endocarditis following revision of the guidelines. However, the number of patients who had dental treatment in the preceding three months was low both before and after the revision. The study concluded that changes in the guidelines had not resulted in any increase in streptococcal infective endocarditis, but no specific conclusions were made regarding the efficacy of antibiotic prophylaxis for dental treatment.[30]

Two studies in England[31,32] have investigated the impact of the recommendation to cease prophylaxis. From 2000 to 2008, before the guidelines were changed, there had been a steady increase in cases of infective endocarditis as well as cases 'possibly' attributable to oral streptococci. The rate of increase in infective endocarditis did not alter significantly in the 25 months after introduction of the new guidelines.[31] However, despite a 78.6% reduction in prescriptions for antibiotic prophylaxis, there were still approximately 2000 prescriptions per month during that time. More than 90% were from dentists, suggesting that they were still prescribing prophylaxis to patients at high risk of infective endocarditis.

This possibility was supported by a subsequent survey[33] four years after the guidelines changed. It found that 36% of dentists had provided antibiotic prophylaxis and one-third had treated patients who had taken prophylaxis prescribed by a medical practitioner. The survey also found that the majority of infectious diseases physicians and cardiologists and 25% of the dentists thought that patients with prosthetic heart valves should receive antibiotic prophylaxis for dental treatment despite the guidelines to the contrary.[33]

In contrast with the short-term English study,[31] the more recent study[32] found that five years after the guidelines

changed, there had been a significant increase in the incidence of infective endocarditis. The investigators were unable to identify the number of cases caused by viridans streptococci and the results were confounded by residual prescribing of antibiotic prophylaxis, with an average of more than 1300 prescriptions per month in the last six months of the study.[32]

The earlier English study[31] had been interpreted as evidence that antibiotic prophylaxis was unnecessary for patients at risk of infective endocarditis undergoing invasive dental procedures. However, the more recent study[32] has been interpreted as evidence that antibiotic prophylaxis is necessary for at-risk patients.[34] Both studies have methodological deficiencies that make it impossible to arrive at a cause-and-effect conclusion in relation to antibiotic prophylaxis and infective endocarditis caused by dental procedures.

Current guidelines

Expert committees around the world have recently issued updated guidelines. In the UK, NICE concluded that there was insufficient evidence to change its existing guidelines and it continues to recommend no routine antibiotic prophylaxis for dental treatment for patients at risk of infective endocarditis.[35] In contrast, expert committees in Europe,[36] the USA[37] and Australia,[38] despite assessing the same evidence as NICE, continue to recommend antibiotic prophylaxis in selected patients (see Box).

The NICE guidelines have continued to attract opposition in the UK.[34,39] Concerns have been expressed that by following the NICE guidelines, rather than the European guidelines, an extra 419 cases of infective endocarditis could occur per year in the UK including a possible 66 extra deaths.[34]

There have also been claims that NICE has incorrectly calculated the risk of deaths from anaphylaxis if antibiotic prophylaxis is given. No cases of fatal anaphylaxis with amoxicillin prophylaxis were reported in the UK during 1972–2007.[40] There were also no reported cases of fatal anaphylaxis in the USA.[18] In contrast, an investigation of the use of oral clindamycin for prophylaxis in England found a significant risk. There were 15 fatalities during 1969–2014, mostly due to *Clostridium difficile* infection.[41]

No clinical trials have yet been published to validate whether antibiotic prophylaxis for invasive dental procedures, for example extractions, can provide significant protection against infective endocarditis in at-risk patients. Australian dentists and medical practitioners are therefore advised to follow the current guidelines published in Therapeutic Guidelines: Antibiotic[38] (see Box) which follow closely the guidelines recommended in the USA[37] and Europe.[36] These are to give amoxicillin, or ampicillin, before the procedure. Cefalexin is recommended for patients hypersensitive to penicillin, unless they have a history of immediate hypersensitivity in which case clindamycin is used.[38]

Prosthetic joint infection

Bacteraemia caused by dental procedures has been considered a surrogate measure of the risk of prosthetic joint infection.[42] As a consequence, there has been a long history of antibiotic prophylaxis for dental procedures despite a lack of evidence for oral *Streptococcus* species being significantly involved in prosthetic joint infection.[43] The overall infection rate for prosthetic joints is approximately 1.5% with the main infecting organism being the skin commensal staphylococci.[42]

Evolution of prophylaxis guidelines

Differing protocols have been published over the years regarding antibiotic prophylaxis for dental treatment of patients with prosthetic joints. The recommended intervals during which prophylaxis should be given have ranged from the first three months to the first two years after joint replacement.[43]

In Australia, guidelines published in 2005 by the Arthroplasty Group of the Australian Orthopaedic Association in conjunction with the Australian Dental Association recommended that prophylaxis was not required for dental treatment, including extraction, after three months in a patient with a normally functioning prosthetic joint.[44] For immunocompromised patients, consultation with the patient's treating physician was advised. However in 2010 Therapeutic Guidelines: Antibiotic stated that for patients with prosthetic joints: 'prophylaxis is not recommended as risks of adverse effects outweigh

Box Cardiac conditions for which antibiotic prophylaxis is recommended for dental treatment in Australia

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair

Previous infective endocarditis

Congenital heart disease *but only* if it involves:

- unrepaired cyanotic defects, including palliative shunts and conduits
- completely repaired defects with prosthetic material or devices, whether placed by surgery or catheter intervention, during the first six months after the procedure (after which the prosthetic material is likely to have been endothelialised)
- repaired defects with residual defects at or adjacent to the site of a prosthetic patch or device (which inhibits endothelialisation)

Rheumatic heart disease in patients at high risk of endocarditis (indigenous Australians and those at significant socioeconomic disadvantage)

Heart transplant patients (consult the patient's cardiologist for specific recommendations)

Source: Reference 38

the benefits of prophylaxis'.[45] Despite these guidelines, some orthopaedic surgeons continued to require that patients with no significant medical history and a healthy, functioning prosthetic joint must receive lifetime antibiotic prophylaxis for all dental visits.

Current guidelines

In 2012, an expert committee of the American Academy of Orthopaedic Surgeons and the American Dental Association reviewed the available evidence on dental treatment and prosthetic joint infection.[42] Only one study satisfied the search criteria.[4] This case-control study found that dental procedures are not risk factors for subsequent prosthetic joint infection and that antibiotic prophylaxis does not reduce the risk of infection. A clinical practice guideline was published recommending that: 'The practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures'.[42]

The wording of this recommendation created some confusion among dentists so an expert panel was therefore convened. It concluded that the evidence in relation to hip and knee prosthetic joints could be extrapolated to all joints on the basis of the morphological and physiological characteristics of the tissues involved.[46] The guideline was amended to read: 'In general, for patients with prosthetic joint implants, prophylactic antibiotics are not recommended prior to dental procedures to prevent prosthetic joint infection'.[46]

Currently, antibiotic prophylaxis for patients with prosthetic joints who are undergoing dental treatment is not routinely recommended in Australia,[38] the USA,[42] Canada,[47] the UK[48] or New Zealand.[49]

Choosing when to prescribe prophylaxis

In situations where a patient has a significant immunodeficiency or an already infected prosthetic joint, the dentist should discuss the situation not only with the orthopaedic surgeon, but also with the physician managing the patient to determine the need for appropriate prophylaxis.

What should a prescriber do if an orthopaedic surgeon insists that a healthy patient with a healthy prosthetic joint must receive antibiotic prophylaxis for dental treatment? The dentist should discuss the patient's medical status and planned dental treatment with the orthopaedic surgeon. If the orthopaedic surgeon recommends prophylaxis but the dentist considers that it is not recommended based on the guidelines, then the orthopaedic surgeon should be invited to prescribe antibiotic prophylaxis and thus be responsible for any adverse outcomes which might result from use of the antibiotic. The patient must be fully informed of the existing guidelines and a clear explanation given for the dentist's decision not to recommend antibiotic prophylaxis.

Currently, antibiotic prophylaxis for patients with prosthetic joints who are undergoing dental treatment is not routinely recommended in Australia

Conclusion

In Australia, expert opinion recommends antibiotic prophylaxis for dental treatment to prevent infective endocarditis in patients with specific cardiac risk factors receiving specific dental treatments. However, antibiotic prophylaxis is not recommended routinely for patients with prosthetic joints.

All guidelines for prophylaxis stress the importance of optimising dental health before the placement of cardiac or orthopaedic prostheses to ensure that no dental sepsis is present. Patients should then be encouraged and trained to practise good oral hygiene and be advised to have regular dental check-ups to maintain their dental health. <

Conflict of interest: none declared

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ARTICLE

Drug dosing in obese adults

SUMMARY

Drug doses often warrant adjustment in obese patients.

Clinicians should consider the patient's body composition when calculating doses. Drug clearance is greater in obesity and correlates with lean body weight.

Body size metrics help guide dose selection, but there are advantages and disadvantages to all of them.

Chronic dosing using total body weight can lead to drug toxicity.

Studies evaluating weight-based dosing strategies are required for many drugs.

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Introduction

In Australia and internationally, approximately 30% of adults are obese, and 65% are either overweight or obese.[1,2] There is little evidence and guidance on how best to dose these individuals.

Few studies have quantified the influence of body size on the pharmacokinetics or pharmacodynamics of many common drugs.[3] Generally, licensed dosing recommendations are based on clinical trials in which people with obesity are under-represented or excluded and evidence-based dosing guidelines are lacking.[3] This may result in arbitrary dose selection leading to therapeutic failure or drug toxicity.

A fixed strategy in which all patients receive the same dose remains a common form of drug dosing. However, significant variations in pharmacokinetic and pharmacodynamic responses can occur between patients due to weight, age, genetics, concurrent diseases and other factors.[4-7] Ideally, the 'one dose fits all' paradigm should be replaced by individualised dosing methods.

Drug doses are usually calculated using a patient's total body weight. This is often inappropriate for obese patients, and clinicians may therefore dose using an alternative body size descriptor. Close monitoring of the patient's clinical response and therapeutic drug monitoring (if available) is important.

Drugs that commonly require dose adjustment in obese patients include low-molecular-weight heparins,[8] aminoglycoside antibiotics,[9] some anaesthetics,[10] monoclonal antibodies and chemotherapeutics.[11]

Body weight

Body size is typically defined using body mass index (BMI) (Table 1).[2] It is a poor dosing metric as comparable BMIs often represent dissimilar body compositions. However, BMI can be used as a guide and clinicians should start to reconsider drug dosing in patients with a BMI over 30.

Pharmacokinetics of drugs in obesity

Without evidence to guide drug dosing in extreme body size, scientific (and physiologically informed) methods rely on an understanding of how body composition influences the pharmacokinetics and pharmacodynamics of drugs. Volume of distribution is important for determining the loading dose and clearance is important to determine the maintenance dose.

Body composition and drug clearance

Body composition changes with total body weight. Normal-weight patients have a total body weight consisting of lean and adipose body weight in an approximate 4:1 ratio. In obese patients, the excess adipose weight is accompanied by a 20–40% increase in lean body weight. This results in a lean:adipose weight ratio of approximately 3:2 (see Fig.).

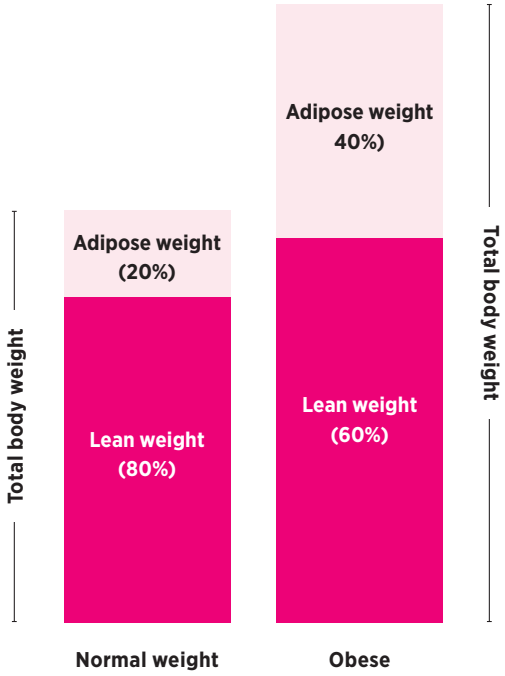
Table 1 **Categorisation of body mass index**

Category	Body mass index (kg/m²)
Normal weight	18.5–24.99
Overweight	25–29.99
Obese class I	30–34.99
Obese class II	35–39.99
Obese class III*	≥40

* The term morbid obesity is synonymous with the definition of obese class III.

Source: Reference 2

Fig. **Body composition in a normal-weight and obese patient**



A pictorial comparison of a normal-weight patient (~BMI 25 kg/m^2) and an obese patient (~BMI 30 kg/m^2) highlighting the approximate proportions of lean and adipose weight.

Drug clearance represents the functional capacity of the body to metabolise and excrete a drug. Clearance is correlated to lean rather than adipose weight as adipose tissue has little metabolic activity.[12]

As clearance determines a drug's maintenance dose, clinicians should consider how lean body weight, rather than total body weight, impacts dosing. When lean body weight increases there will be a corresponding increase in drug clearance and an increased dose may be required.

Commonly used weight-based drugs that may require dose adjustment and monitoring in obesity, and in particular morbid obesity, are listed in Table 2. Individual drug monographs in the Australian Medicines Handbook should be consulted to identify if weight-based dosing is required.

Clearance has been correlated with lean body weight for opioids such as fentanyl,[10] anaesthetics such as propofol,[10] ranitidine, lithium and enoxaparin.[8]

Volume of distribution

Volume of distribution is related to structural aspects of the body. Hydrophilic drugs generally have a high plasma concentration relative to dose, and a smaller volume of distribution. In contrast, lipophilic drugs distribute more readily into adipose tissue, resulting in lower plasma concentrations and a larger volume of distribution.

Table 2 **Drugs that require dose adjustment in obesity**

Drug	Patient monitoring*
Low-molecular-weight heparins (enoxaparin, dalteparin)	TDM – anti-Xa monitoring, clinical response
Digoxin	TDM – serum digoxin, clinical response
Phenytoin	TDM – serum phenytoin, clinical response
Aciclovir	clinical response
Antibiotics – macrolide (e.g. erythromycin†), fluoroquinolone (e.g. ciprofloxacin†)	clinical response, microbiological response
Antibiotics – glycopeptides (e.g. vancomycin), aminoglycosides (e.g. gentamicin, tobramycin), beta-lactams† (e.g. penicillins, cephalosporins)	TDM – all, clinical response, microbiological response
Antifungals (e.g. amphotericin, voriconazole, fluconazole)	TDM – serum voriconazole, clinical response, microbiological response
Unfractionated heparin	TDM – aPTT monitoring, clinical response
Monoclonal antibodies	TDM – clinical response
Ciclosporin	TDM – serum ciclosporin, clinical response

TDM therapeutic drug monitoring aPPT activated partial thromboplastin time
* Response refers to both effectiveness (e.g. cure) or adverse effects.
† Dose adjustment is generally required at high intravenous doses.

Hydrophilic drugs (e.g. aminoglycosides, lithium, aciclovir, glycopeptides, beta-lactams, low-molecular-weight heparins) typically remain in extracellular fluid and their volume of distribution correlates with lean mass. This implies that the distribution of hydrophilic drugs should not be significantly influenced by excess adipose tissue.

For lipophilic drugs, volume of distribution is more likely to correlate with total body weight.[6] Highly lipophilic drugs (phenytoin, midazolam, voriconazole, propofol) distribute extensively into adipose tissue, resulting in a larger volume of distribution compared to less lipophilic drugs.

Drugs with a large volume of distribution often require loading doses followed by a constant dose rate to maintain steady-state plasma concentrations. Steady-state concentrations are dependent on drug clearance.

Body size descriptors used to calculate drug doses

Several different body descriptors can be used to calculate drug doses (Table 3).[13-16]

Total body weight

Using total body weight assumes that the pharmacokinetics of the drug are linearly scalable from normal-weight patients to those who are obese. This is inaccurate. For example, we cannot assume that a 150 kg patient eliminates a drug twice as fast as a 75 kg patient and therefore double the dose. Clinicians are alert to toxicities with higher doses, for example nephro- and neurotoxicity with some antibiotics and chemotherapeutics, and bleeding with anticoagulants. Arbitrary dose reductions or 'caps' are used to avoid these toxicities, but if too low can result in sub-therapeutic exposure and treatment failure.[6,11,12]

Lean body weight

Using a lean body weight metric encompasses a more scientific approach to weight-based dosing. Lean body weight reflects the weight of all 'non-fat' body components, including muscle and vascular organs such as the liver and kidneys. As lean body weight contributes to approximately 99% of a drug's clearance,[5] it is useful for guiding dosing in obesity.

This metric has undergone a number of transformations. The most commonly cited formula derived by Cheymol[7] is not optimal for dosing across body compositions and can even produce a negative result. A new formula has been developed (see Table 3) that appears stable across different body sizes, in particular the obese to morbidly obese.[15]

A practical downfall of the calculation of lean body weight (and other body size descriptors) is the numerical complexity, which may not be palatable to a busy clinician. Often limited time is available for prescribing and an immediate calculation is required. Lean body weight calculators are available online, for example in the Therapeutic Guidelines.[17]

Adjusted body weight

Calculating doses based on adjusted body weight is mainly used for aminoglycoside antibiotics.[14] It was developed to account for adipose tissue, which does not affect drug clearance. A correction factor of 0.4 is used to estimate adjusted body weight (Table 3). The aminoglycosides dose is then calculated using the resultant weight. This descriptor is rarely used in other drug classes, although there is some evidence for other antibiotics in the morbidly obese.[9,14]

Body surface area

Body surface area[16] is traditionally used to dose chemotherapeutics. It is a function of weight and height and has been shown to correlate with cardiac output, blood volume and renal function. However, it is controversial in patients at extremes of size because it does not account for varying body compositions. As a consequence, some older drugs such as cyclophosphamide, paclitaxel and doxorubicin were 'capped' (commonly at 2 m^2) potentially resulting in sub-therapeutic treatment.[11] Recent guidelines suggest that unless there is a justifiable reason to reduce the dose

Table 3 **Body size descriptors commonly used in drug dosing**

Name	Formula
Total body weight (kg)	–
Ideal body weight (kg)[13]	45.4 + 0.89 x (height (cm) – 152.4) + (4.5 if male)
Adjusted body weight (kg)[14]	Correction factor* x (TBW – IBW) + IBW
Lean body weight (kg)[15]	
males	$\frac{9270 \times \text{TBW (kg)}}{6680 + 216 \times \text{BMI (kg/m}^2\text{)}}$
females	$\frac{9270 \times \text{TBW (kg)}}{8780 + 244 \times \text{BMI (kg/m}^2\text{)}}$
Body surface area (m^2)[16]	$\sqrt{\frac{\text{height (cm)} \times \text{TBW}}{3600}}$

TBW total body weight
IBW ideal body weight
BMI body mass index
* Correction factor is 0.4 for aminoglycosides.

(e.g. renal disease), total body weight should be used in the calculation of body surface area, until further research is done.[11] Little research into dosing based on body surface area has been conducted for other medicines.

Ideal body weight

Ideal body weight was developed for insurance purposes not for drug dosing.[13] It is a function of height and gender only and, like body surface area, does not take into account body composition. Using ideal body weight, all patients of the same height and sex would receive the same dose, which is inadequate and generally results in under-dosing.[4] For example a male who has a total body weight of 150 kg and a height of 170 cm will have the same ideal body weight as a male who is 80 kg and 170 cm tall. Both could potentially receive a mg/kg dose based on 65 kg (ideal body weight).

Calculating drug doses

The clinical issue is that calculating drug doses using each body size descriptor will result in a different weight. Consider dosing a 150 kg man who is 170 cm tall. Rounded to the nearest 5 kg, his body size descriptors are:

- total body weight = 150 kg
- lean body weight = $(9270 \times 150) / 6680 + 216 \times (150/1.7^2) = 80$ kg
- ideal body weight = $45.4 + 0.89 \times (170 - 152.4) + 4.5 = 65$ kg

Obviously, large variations exist for mg/kg dosing depending on which metric is used.

Enoxaparin

A pertinent example of this dilemma is enoxaparin, a hydrophilic anticoagulant. Its licensed dose for treatment of venous thromboembolism is based on total body weight (mg/kg). Many clinicians recognise that this results in high doses in obesity and increases the risk of toxicity, so they reduce or cap the dose (often at 100 mg) in patients over 100 kg.[18] This may result in sub-therapeutic anti-Xa concentrations, particularly in morbid obesity, as clearance increases with body size.

A dose based on lean body weight is warranted in this case and a dose of 1.5 mg/kg (lean body weight) has been proposed.[8] In the above example, the 150 kg male would receive 120 mg twice daily (rounded up), that is 1.5 x 80 kg.

The prophylactic dose is usually 20–40 mg daily. As clearance increases with body size, the dose should be increased in morbid obesity and suggested doses include 30–40 mg twice daily.[19]

Unfractionated heparin

In thrombotic diseases, unfractionated heparin is dosed using total body weight. An initial bolus (units/kg) is followed by a continuous infusion (units/kg/hour) and adjusted based on the activated partial thromboplastin time (aPTT). However, nomograms often use a dose cap (bolus and maintenance) in obese patients. This can lead to undertreatment, and increased monitoring is recommended. Like enoxaparin, the prophylactic dose should be increased in morbid obesity, for example 5000 units three times a day or 7500 units twice daily.

Carvedilol, apixaban, ribavirin and prasugrel

Some drugs have a licensed dichotomised dose based on total body weight. The maximum daily dose of carvedilol is 50 mg in patients weighing less than 85 kg and 100 mg for patients weighing 85 kg or more. Consequently a patient weighing 86 kg would receive twice the dose of a patient weighing 84 kg. Dichotomised dose strategies can result in under- and overdosing and should be used with caution in patients with obesity. Apixaban, ribavirin and prasugrel have similar dosing recommendations.

Cephazolin

Cephalosporins are often prescribed as surgical prophylaxis. Due to the increase in clearance in obese patients, the dose should be increased.[9] The recommended dose of 1 g has been increased to 2 g in obese patients to ensure adequate exposure and may need to be administered more frequently.

Conclusion

Estimating the optimal dose for obese patients is difficult and, in many cases, ill defined. Basing maintenance doses on total body weight is unlikely to result in a comparable drug response across different body sizes and generally increases the risk of adverse events. Individualised dosing based on the patient's lean body weight is recommended, with accompanying therapeutic drug monitoring and monitoring of the patient's clinical response.

Designing clinical trials that stratify doses across a range of body weights will improve drug-dosing knowledge. In the meantime, we need to rely on scientific principles to dose many drugs in the obese. <

Conflict of interest: none declared

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FURTHER READING

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ARTICLE

Access to unregistered drugs in Australia

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Authorised Prescriber Scheme, drug regulation, personal importation, Special Access Scheme, unapproved products

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SUMMARY

Drugs can usually only be prescribed for patients if they have been approved by the Therapeutic Goods Administration for inclusion in the Australian Register of Therapeutic Goods.

Unregistered drugs can be obtained through the Special Access Scheme, the Authorised Prescriber Scheme or by personal importation.

Almost any drug can be accessed through these schemes, if it is considered clinically justified.

The use of unregistered drugs should be considered experimental. Written informed consent from the patient is therefore required and any adverse events need to be reported to the Therapeutic Goods Administration.

Introduction

Before a drug can be supplied to patients in Australia, it must undergo evaluation by the Therapeutic Goods Administration (TGA). If its safety and efficacy, and the quality of its manufacture are satisfactory, it can be included in the Australian Register of Therapeutic Goods. A drug might not be registered in Australia if it is new and there has not yet been time for it to be evaluated by the TGA, or the manufacturer has elected not to have the drug registered in Australia.

In certain circumstances, Australian legislation allows patients to access drugs that are not included in the Australian Register of Therapeutic Goods. Unregistered drugs can be obtained through:

- the Special Access Scheme
- the Authorised Prescriber Scheme
- importation for personal use
- clinical trials.[1]

Almost any drug can be obtained via these schemes, except those for which the manufacture, possession, sale or use are prohibited by law (e.g. illicit drugs).

Special Access Scheme

The Special Access Scheme allows for the importation and supply of an unregistered drug for an individual patient under the supervision of a medical practitioner, on a case-by-case basis.[2] This is the most common scheme used by GPs. Circumstances when patient access to an unregistered drug may be appropriate include:

- experimental or investigational products for terminally ill patients
- a drug that has been taken by a patient in a clinical trial, but has not yet received TGA approval
- drugs available overseas, but not marketed in Australia (including when a similar registered product is in short supply in Australia).[3]

Typically, drugs accessed through this scheme are infrequently used and are often for uncommon conditions. The Table shows examples of drugs that have been accessed through the Special Access Scheme at our hospital.

Until July 2017 the Special Access Scheme had two categories of patients.[3] Category A patients were defined as 'persons who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment.' Everyone else was in category B and this was probably the category most used by GPs. Each year there were approximately 40 000 category A and 20 000 category B applications made to the TGA.

Following a policy review[4], a new category was added in July 2017. Category C enables specified types of health professional to prescribe from a list of unapproved drugs that have an established role in the treatment of particular conditions. There are separate lists for drugs, biologicals and devices. Drugs that are not listed in category C are deemed to be higher risk and remain in category B. The TGA has developed an online tool to help prescribers decide which category is appropriate for their patients.

Applications

To obtain a drug through the Special Access Scheme, an application or notification needs to be made to the TGA. Forms are available from the TGA website (www.tga.gov.au/form/special-access-scheme), and completed forms are emailed (SAS@tga.gov.au) or faxed to the TGA.[2]

For category A patients, the prescriber does not need to seek approval from the TGA in advance. A completed 'Special Access Scheme – Category A' form is sent to the supplier (which provides them with the legal authority to supply the product), with a copy of the form to be forwarded to the TGA within four weeks.[3]

For a category B patient, an application to the TGA needs to be completed in advance. An unregistered drug cannot be supplied before the TGA has evaluated and approved the application.[3]

When assessing applications, the TGA takes into consideration whether there is sufficient justification to approve supply of the drug. This includes whether there are registered products already available to treat the patient's condition, whether these products have been tried by the patient in the past, and the seriousness of the patient's condition.[3] In addition, the TGA considers the degree and quality of evidence to support the drug's efficacy and safety. For example, greater credence is placed on evidence from published randomised trials over individual case reports or expert opinion.[3] The TGA also considers the relevance of the qualifications of the requesting prescriber in relation to the drug being requested.

For the drugs listed in category C, such as melatonin modified-release tablets for the treatment of sleep disorders, preapproval is not necessary. However, the category C form must be used to notify the TGA within four weeks of supplying the drug.

Supply

Unregistered drugs may be available from suppliers within Australia, in which case the prescriber (or pharmacy) needs to contact the supplier directly. However, if the drugs are unavailable, the requesting doctor may need to source them from overseas. When this is the case, the prescriber needs to check whether the importation of a drug is controlled by customs regulations.[3,5] Examples of drugs that are subject to these regulations include:[3,5]

- drugs of abuse, for example narcotics, amphetamines, psychotropic substances
- substances that may be considered performance enhancing for athletes, for example anabolic steroids, erythropoietin, growth hormones
- antibiotics.

Drugs subject to these regulations cannot be imported without permission. It is important to note that the import permit and, when required, an import licence for drugs such as narcotics and medical cannabis are obtained through the Office of Drug Control. This process is separate from the TGA's approval.[5]

Table **Unregistered products obtained by a Queensland hospital**

Drug	Condition
Special Access Scheme category A	
Ceftazadime-avibactam	Multiresistant infection
Artesunate	Malaria
Diazoxide	Insulinoma
Special Access Scheme category B	
Midodrine	Orthostatic hypotension
Rufinamide	Seizures related to Lennox-Gastaut syndrome
Benzbromarone	Gout
Mexilitine	Chronic neuropathic pain
Special Access Scheme category C	
Paromomycin	Amoebic liver abscess
Pristinamycin	Multiresistant infection
Tetracycline	Resistant *Helicobacter pylori* infection
Melatonin	Sleep disorders

Consent

The use of unregistered drugs should be considered experimental. It is a condition of the Special Access Scheme that the patient (or their legal guardian) provides written informed consent.[3] This needs to be provided freely and the patient must understand the nature of their condition (including its natural history) and have appropriate knowledge of the treatment options. Specifically, the patient must be informed about:

- the product not being approved in Australia
- the possible benefits of treatment and any known risks and adverse effects
- the possibility of unknown risks and late adverse effects
- any available alternative treatments using registered products.[3]

It is important for both the patient and prescriber to understand that the Australian Government does not accept responsibility for any adverse consequences of treatment, including any defects in the product related to manufacture. In addition, the prescriber of an unregistered drug is required to report the details of any actual or suspected adverse drug reactions to the TGA within 15 days.[3] Specific information about the unregistered drug may not be readily available, as the product information for

the unregistered drug will not be in MIMS and may be limited in the Australian Medicines Handbook. If the drug is registered in another jurisdiction, product information may be available from the US Food and Drug Administration or the European Medicines Agency.

Authorised Prescriber Scheme

The Authorised Prescriber Scheme also allows access to almost any unregistered drug for particular patient groups. An Authorised Prescriber is a medical practitioner who has been approved by the TGA to prescribe an unregistered drug to a group of patients for a specific indication, without the need for individual TGA approval.[6] In addition to all the requirements and responsibilities of the prescriber under the Special Access Scheme (including the need for written informed consent from the patient and the reporting of adverse drug events) the doctor requires the endorsement of an ethics committee or relevant specialist college before they can be approved as an Authorised Prescriber.[6] The use of carboprost as a treatment for postpartum haemorrhage by an obstetrician is a potential example where the Authorised Prescriber Scheme might be appropriate.

The requirement to submit a clinical justification for evaluation by the TGA was removed in July 2017. These reforms also increased the duration of approval for drugs from two to five years. Authorised Prescribers have to report every six months how many patients they are treating with the unregistered drug.

Personal importation

Personal importation occurs when:

- an individual either brings a therapeutic good into Australia on their person or arranges from within Australia for a therapeutic good to be sent to them from an overseas supplier
- the goods are to be used by that individual or a member of their immediate family and are not sold or supplied to any other person.[7]

For personal importation, the quantity imported on any given occasion cannot exceed three months treatment and no more than 15 months supply can be obtained per year. There are limitations on the type of drugs that can be accessed via personal importation. It is prohibited to import drugs subject to customs regulations (e.g. drugs of abuse, anabolic or androgenic steroids, erythropoietin, growth hormones, gonadotrophins and antibiotics). In these cases, the patient's treating doctor is required to obtain supply under the Special Access Scheme. In addition, with the exception of insulin, the personal importation of an injectable product containing material of human or animal origin is prohibited. For prescription drugs (e.g. Schedule 4 or 8), a prescription issued by a medical practitioner registered in Australia (or alternatively, an import licence) is required.

As with accessing non-approved drugs through other means, there can be no guarantees of the quality, safety and efficacy of the imported product. Patients must be prepared to accept the potential harms and benefits of its use.[7]

Clinical trials

Obtaining a drug as part of a clinical trial requires ethics committee approval and either TGA approval or notification.[8]

Conclusion

Drugs that are not included in the Australian Register of Therapeutic Goods can be accessed by patients, when clinically justified, via the Special Access Scheme, the Authorised Prescriber Scheme or personal importation. Written informed consent from the patient is required for all unregistered drugs as their use should be considered experimental. More information can be obtained from the TGA website (www.tga.gov.au/accessing-unapproved-products). <

Conflict of interest: none declared

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New drugs

Brexpiprazole

Aust Prescr 2017;40:197–8
https://doi.org/10.18773/austprescr.2017.064
First published 15 August 2017

Approved indication: schizophrenia

Rexulti (Lundbeck)
0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg tablets
Australian Medicines Handbook section 18.2

Brexpiprazole is a new antipsychotic for schizophrenia. It is structurally similar to aripiprazole and has a similar mechanism of action. It acts at many receptors. For example, it is a partial agonist at serotonin 5-HT_{1A} and dopamine D_2 and D_3 receptors and an antagonist at the serotonin 5-HT_{2A} and noradrenergic receptors.

Two six-week randomised, placebo-controlled trials investigated the safety and efficacy of brexpiprazole in 1310 patients with acute schizophrenia (see Table).[1,2] The primary outcome measure was improvement on the Positive and Negative Syndrome Scale (PANSS). This is a 30-item scale assessing positive (e.g. delusions, hallucinations), negative (e.g. emotional withdrawal) and general symptoms (e.g. anxiety, depression). In one trial, mean improvements in the PANSS scores after treatment were significantly higher with brexpiprazole 2 mg/day and 4 mg/day than with placebo.[1] However, in the other trial, only the 4 mg/day dose was significantly better than placebo.[2]

Another efficacy measure was response rate. This was defined as the proportion of patients with a ≥30% improvement in their PANSS score or Clinical Global Impression (CGI) score. In the trials, 46.1–49.7% of patients had responded to the 4 mg/day dose compared with 30.3–31.7% in the placebo groups (see Table).[1,2]

In another trial, flexible doses of open-label brexpiprazole (1–4 mg/day) and aripiprazole (10–20 mg/day) were compared in 97 patients with acute schizophrenia. After six weeks of treatment, mean changes in PANSS scores with brexpiprazole were comparable to aripiprazole (see Table).[3]

A longer term trial assessed brexpiprazole as a maintenance treatment for schizophrenia in patients who had been stabilised on brexpiprazole.[4] These patients were randomised to 52 weeks of brexpiprazole 1–4 mg/day (97 patients) or placebo (105 patients). The primary outcome was time between randomisation and exacerbation of psychotic symptoms or impending relapse. At the interim analysis, time to impending relapse was significantly delayed in the brexpiprazole group compared to the placebo group (hazard ratio 0.292, 95% confidence interval 0.156–0.548, p<0.0001) and the trial was terminated. As the trial was cut short, only 23 patients completed 52 weeks of treatment.[4]

Tolerance to brexpiprazole after short- and long-term exposure was assessed in a safety study.[5] In short-term studies of patients taking up to 6 mg/day brexpiprazole (n=1256), akathisia (5.8%) and gain in weight of more than 7% (4.7%) were more frequently reported with brexpiprazole than with placebo.[5] These effects appeared to be dose-related. Newly diagnosed metabolic syndrome was also more common with brexpiprazole than with placebo in the short-term trials (1.2% vs 0.8%), and was even higher in the longer term trials (3.1%). Of the patients who took the drug for a year or more, 5.6% gained at least 15 kg in weight.[5] Brexpiprazole did not increase the QT interval in the trials.

Brexpiprazole has not been tested during pregnancy. However, exposure to other antipsychotics during the third trimester increases the risk of extrapyramidal or withdrawal symptoms in neonates. In animal studies, brexpiprazole did not have teratogenic effects.

Brexpiprazole can be taken with or without food. The starting dose is 1 mg. This should be titrated to the recommended target dose of 2–4 mg over eight days depending on clinical response and tolerability. In people with moderate–severe hepatic or renal impairment, the maximum recommended daily dose is 3 mg.

After oral administration, peak plasma concentrations are reached within four hours. The terminal half-lives of brexpiprazole and its major metabolite are 86–91 hours. Approximately 25% of the dose is excreted in urine and 46% in faeces.

Brexpiprazole is mainly metabolised by cytochrome P450 (CYP) 3A4 and CYP2D6. Strong CYP3A4 inhibitors, such as ketoconazole, increase serum concentrations of brexpiprazole, while inducers (e.g. rifampicin) reduce concentrations so adjustment of the brexpiprazole dose is required with concomitant dosing. Dose reduction is recommended in patients who are poor CYP2D6 metabolisers.

The 4 mg/day dose of brexpiprazole seems to be effective for acute schizophrenia in short-term trials. Up to half of the patients responded to this dose.[1,2] In a longer term placebo-controlled trial, brexpiprazole reduced the risk of relapse in patients already established on brexpiprazole.[4] As with

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

NEW DRUGS

Table **The efficacy of brexpiprazole for acute schizophrenia in six-week trials**

Correll et al. 2015 [1]

	Placebo	brexpiprazole/day		
		0.25 mg	2 mg	4 mg
Number of patients	184	90	182	180
Mean baseline PANSS score	95.9	93.4	95.9	94.9
Mean improvement in PANSS score	12.0	14.9	20.7*	19.7*
Response rate†	30.3%	39.1%	47.8%	46.1%

Kane et al 2015 [2]

	Placebo	brexpiprazole/day		
		1 mg	2 mg	4 mg
Number of patients	184	120	186	184
Mean baseline PANSS score	94.8	93.3	96.3	95.1
Mean improvement in PANSS score	13.5	16.9	16.6	20*
Response rate†	31.7%	43.6%	38.6%	49.7%

Citrome et al 2016 [3]

	brexpiprazole 1–4 mg/day	aripiprazole 10–20 mg/day
Number of patients	64	33
Mean baseline PANSS score	94.1	93.3
Mean improvement in PANSS score	22.9	19.4
Response rate†	60.9%	48.5%

PANSS Positive and Negative Syndrome Scale
* statistical significance over placebo
† proportion of patients with a ≥30% improvement in their PANSS score or Clinical Global Impression (CGI) score after 6 weeks treatment

other antipsychotics, akathisia and weight gain are common. Brexpiprazole has been approved as an adjunct treatment of major depression in the USA but not in Australia.

TT manufacturer provided additional useful information

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

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

Pegvisomant

Approved indication: acromegaly

Somavert (Pfizer)

vials containing 10 mg, 15 mg and 20 mg as powder for reconstitution

Australian Medicines Handbook section 10.6

Aust Prescr 2017;40:199
https://doi.org/10.18773/austprescr.2017.065
First published 1 September 2017

Acromegaly is usually the result of an adenoma in the anterior pituitary gland. Although the high concentrations of growth hormone can have direct effects, they also act by increasing production of insulin-like growth factors. A high concentration of insulin-like growth factor type 1 (IGF-1) is a diagnostic feature of acromegaly.

Most patients are treated with surgery, sometimes followed by radiotherapy. Medical treatment may be needed if the surgery is not successful. Giving an analogue of somatostatin (growth hormone inhibiting peptide) is one approach and lanreotide and octreotide have been available for many years.[1]

Pegvisomant offers a different approach. It is an analogue of growth hormone, but it has been genetically engineered to act as a growth hormone receptor antagonist. By binding to the receptor, pegvisomant blocks the binding of growth hormone. This is reflected in reduced concentrations of IGF-1.

The protein is given by subcutaneous injection reaching peak serum concentrations in the next 33–77 hours. As the molecule is pegylated (with polyethylene glycol polymers) its clearance is reduced. The half-life is approximately six days. A daily injection is recommended with the dose adjusted according to the IGF-1 concentration.

A double-blind study compared three different doses of pegvisomant with placebo in 112 patients, 93 of whom had already had surgery for their pituitary adenomas. After 12 weeks the concentration of IGF-1 had significantly declined in the three groups given pegvisomant. Most of the reduction occurred within two weeks.[2]

In an observational uncontrolled longer term follow-up study, 87 out of 90 patients treated for a year had normal IGF-1 concentrations. The concentrations remained low in 39 patients treated for 18 months.[3]

During the long-term follow-up, headaches and infection were the most frequently reported adverse events. Injection-site reactions affected 11% of patients and two people were withdrawn from the study because of increased concentrations of liver enzymes.[3] Hepatic function should therefore be tested before and during therapy.

Blocking the growth hormone receptor may result in increased growth hormone production to overcome the blockade. This is a concern as the patient's tumour may enlarge. In the follow-up study, in patients who had not received radiotherapy, there was an increase in tumour size, however this was not statistically significant.[3]

Pegvisomant was originally approved in Australia more than a decade ago. During this interval more information about the drug has emerged from overseas studies. The postmarketing, open-label ACROSTUDY involved 710 patients followed for up to five years. Most of these patients had received other treatments before starting pegvisomant monotherapy. Although 67.5% of the patients achieved a normal concentration of IGF-1, and 2.6% had a low concentration, it remained elevated in 29.9%. Adverse events affected 345 patients including 133 who had serious adverse events such as increased tumour size. There were liver-related adverse effects in 30 patients,[4] including eight who had transaminase concentration three times the normal limit.[4] Systemic hypersensitivity reactions have also been reported.[4]

Acromegaly is a rare disease so data are still limited. Pegvisomant is only indicated if patients have an inadequate response to surgery, radiation and other drugs. The ACROSTUDY shows that pegvisomant is less effective at normalising IGF-1 than it appeared to be in the original trials.[2,3] This could possibly explain why many patients could not be managed with pegvisomant monotherapy and why the proportion needing higher doses increased during the study. Although there has been research into less frequent dosing, most patients will need daily injections.[4]

T T T manufacturer provided the (2005) clinical evaluation

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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, and the European Medicines Agency.

NEW DRUGS

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Sofosbuvir with velpatasvir

Approved indication: hepatitis C

Epclusa (Gilead)
tablets containing sofosbuvir 400 mg and velpatasvir 100 mg
Australian Medicines Handbook section 5.5

This is a fixed-dose combination tablet indicated for people with hepatitis C genotypes 1–6. In Australia, approximately 50% of all hepatitis C cases are genotype 1 and 35–40% are genotype 3.

Sofosbuvir is already available in combination with ledipasvir[1] and can be used concomitantly with daclatasvir,[2] peginterferon and ribavirin.[3] It is an inhibitor of the NS5B RNA polymerase and blocks viral replication. Velpatasvir is a newly approved drug. Like ledipasvir and daclatasvir, it inhibits the NS5A protein which is required for assembly and release of viral particles.

The efficacy of this combination has been investigated in four main trials (ASTRAL 1–4, see Table).[4-6] The trials enrolled treatment-naïve and treatment-experienced patients with genotypes 1–6. Compensated liver cirrhosis was allowed in all four studies, but those with decompensated liver disease were only included in ASTRAL-4. The primary efficacy measure in the trials was the proportion of patients who achieved a sustained virologic response. This was defined as undetectable viral RNA in a blood test 12 weeks after the end of treatment.

Almost all patients in ASTRAL-1 (99%) had a sustained response to 12 weeks of treatment with sofosbuvir and velpatasvir. This was irrespective of their hepatitis C genotype, cirrhosis status or previous experience with treatment.[4] No one in the placebo group had a sustained virologic response.

In ASTRAL-2 and ASTRAL-3, sofosbuvir with velpatasvir was compared to treatments for genotype 2 (12 weeks of sofosbuvir plus ribavirin) and genotype 3 infection (24 weeks of sofosbuvir plus ribavirin). Sofosbuvir/velpatasvir was superior to the comparators for both genotypes (see Table).[5]

ASTRAL-4 only enrolled patients with decompensated cirrhosis (Child-Pugh B) infected with genotypes 1–4 and 6. Overall, sustained response rates to 12 weeks of sofosbuvir/velpatasvir were high (83%) and comparable to sofosbuvir/velpatasvir plus ribavirin (94%) and 24 weeks of sofosbuvir/velpatasvir (86%). However on further analysis of the different genotypes, only 50% of patients (13/26) with genotype 3 responded to 12 or 24 weeks of

Table **Efficacy of sofosbuvir/velpatasvir* in chronic hepatitis C**

Trial (design)	Patient characteristics	Genotype	Treatment arm (duration)	Efficacy – patients with SVR12
ASTRAL-1 (double-blind)[4]	Treatment-naïve and experienced patients, with or without cirrhosis	1, 2, 4, 5†, 6	sofosbuvir/velpatasvir (12 weeks)	99% (618/624)
			placebo (12 weeks)	0% (0/116)
ASTRAL-2 (open-label)[5]		2	sofosbuvir/velpatasvir (12 weeks)	99% (133/134)
			sofosbuvir plus ribavirin‡ (12 weeks)	94% (124/132)
ASTRAL-3 (open-label)[5]		3	sofosbuvir/velpatasvir (12 weeks)	95% (264/277)
			sofosbuvir plus ribavirin‡ (24 weeks)	80% (221/275)
ASTRAL-4 (open-label)[6]	Treatment-naïve and experienced patients with decompensated cirrhosis	1–4, 6§	sofosbuvir/velpatasvir (12 weeks)	83% (75/90)
			sofosbuvir/velpatasvir plus ribavirin‡ (12 weeks)	94% (82/87)
			sofosbuvir/velpatasvir (24 weeks)	86% (77/90)
ASTRAL-5 (open-label)[7]	Treatment-naïve and experienced patients co-infected with HIV	1–4	sofosbuvir/velpatasvir (12 weeks)	95% (99/104)

SVR12 sustained virologic response 12 weeks after the end of treatment
* Sofosbuvir 400 mg and velpatasvir 100 mg was given once-daily.
† All 35 patients with genotype 5 infection received sofosbuvir/velpatasvir.
‡ Ribavirin dose was weight-based and given twice-daily.
§ There was only 1 patient with genotype 6 infection.

sofosbuvir/velpatasvir. When ribavirin was added to 12 weeks of sofosbuvir/velpatasvir, 85% (11/13) of people with genotype 3 had a sustained response.[6]

Another trial (ASTRAL-5) enrolled people with genotypes 1–4 who were co-infected with HIV. The overall response rate to 12 weeks of sofosbuvir/velpatasvir was 95%.[7]

In a pooled analysis of ASTRAL 1–3, the most common adverse events in people taking sofosbuvir/velpatasvir were headache (29% of patients), fatigue (21%), nausea (13%) and nasopharyngitis (12%). These occurred at a similar frequency in those receiving placebo in the ASTRAL-1 trial. Anaemia was common in people who received the combination with ribavirin, particularly in patients with decompensated cirrhosis.

Following oral administration, sofosbuvir is absorbed within an hour and velpatasvir within three hours. Absorption of velpatasvir decreases as gastric pH increases therefore antacids should be taken at least four hours before or after sofosbuvir/velpatasvir. H_2 receptor antagonists can be taken at the same time or 12 hours apart. Proton pump inhibitors, comparable to omeprazole 20 mg, can also be taken at the same time as sofosbuvir/velpatasvir and with food.

Sofosbuvir and velpatasvir are substrates of P-glycoprotein and velpatasvir is a substrate of cytochrome P450 (CYP) 2B6, CYP2C8 and CYP3A4. Potent inducers of these (e.g. carbamazepine, efavirenz, rifampicin, St John's wort), may decrease serum concentrations of one or both drugs in the combination and co-administration is not recommended. Sofosbuvir/velpatasvir may increase concentrations of digoxin, tenofovir and rosuvastatin, and close monitoring and possible dose adjustment of these drugs is recommended. Concomitant amiodarone can cause symptomatic bradycardia and is not recommended.

It is not known if sofosbuvir/velpatasvir is safe for pregnant women as there have been no adequate studies. No fetal effects were found at high doses in animal studies. It is not known if sofosbuvir and velpatasvir are excreted in human milk, but both were found in the milk of lactating rats. There were no observed effects on nursing rat pups.

When this combination is used with ribavirin, prescribers should be aware that ribavirin is teratogenic and toxic to embryos and is contraindicated in pregnant women and male partners of pregnant women. Female patients and female partners of male patients must use contraception during and for six months after the end of ribavirin treatment.

Patients must be screened for current or past hepatitis B (surface antigen, core antibody) before starting sofosbuvir/velpatasvir as hepatitis C treatment can cause reactivation of hepatitis B infection.

This fixed-dose combination of sofosbuvir and velpatasvir was effective in eradicating hepatitis C infections caused by genotypes 1–6. For most patients, the recommended dose is one tablet a day for 12 weeks. In those with genotype 3 infection who have compensated cirrhosis, the addition of ribavirin may be considered. Unlike some of the other direct-acting combination drugs for hepatitis C (e.g. elbasvir/grazoprevir,[8] paritaprevir/ritonavir/ombitasvir plus dasabuvir[9]), sofosbuvir/velpatasvir can be used in patients with decompensated liver disease. However, ribavirin should be added to the regimen in these patients. As yet, there are no clinical data for sofosbuvir/velpatasvir in patients with Child-Pugh C cirrhosis or those who have had a liver transplant. This combination is well tolerated but prescribers need to be aware of the numerous drug interactions that can occur.

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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 and the European Medicines Agency.

BOOK REVIEW

Therapeutic Guidelines: Rheumatology. Version 3.

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Aust Prescr 2017;40:202
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Melbourne: Therapeutic Guidelines Limited; 2017.
331 pages
Also available at www.tg.org.au

The complex world of rheumatology can be confusing for those not deeply entrenched in it. It can appear full of obscure diagnoses, tests and treatments. Individual patients can be hard to categorise, and so much of standard practice is rarely articulated. It is therefore of great credit to the authors that this guide is practical and accessible while sacrificing very little in terms of complexity.

It is clear that much more than just the cover has changed for this edition. New sections at the beginning of the text on undifferentiated symptoms and undifferentiated arthritis clearly express the core rheumatological approach for the non-specialist. These additions are concise and will be invaluable to frontline clinicians.

Immunosuppression management, fibromyalgia, back and neck pain, osteoarthritis and the approach to mild non-specific symptoms make up the bulk of queries to specialists from primary care. These are all addressed with updated advice that is accurate but realistic and easy to use. This should be welcomed by both GPs and rheumatologists.

Sections on core rheumatological diseases from previous editions have been bolstered with new evidence. The style of the Therapeutic Guidelines brand, such as highlighted therapeutic options and flowcharts, is helpful. Trustworthy internet resources are also a welcome addition. Sometimes textbooks can be verbose around uncertainty and controversy. However, despite rheumatology being full of these areas, very few words in this book are wasted.

It is often said that rheumatology is not for those who like black and white, but for those who embrace shades of grey. This impressive book gives the non-specialist reader the chance to appreciate these shades quickly and accurately. It should be embraced by specialist trainees and GPs alike.

David Liew is the current editorial registrar on the Editorial Executive Committee of Australian Prescriber.

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ANSWERS TO SELF-TEST QUESTIONS

1 False 2 True
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