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Unpronounceable drug names

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Keywords

medication errors, drug names, drug information

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“Pot-ay-toe, pot-ah-toe. Tom-ay-toe, tom-ah-toe. Let’s call the whole thing off.”

Songwriters George and Ira Gershwin understood the problem of different pronunciations of the same word way back in 1937. At that time, the only patented medicines doctors had to know how to pronounce were aspirin, insulin, penicillin, phenobarbital and sulfanilamide. Today’s prescribers are confronted by ixekizumab, rovalpituzumab, tofacitinib and idelalisib.

Conspiracy theorists might suggest that the generic name of a drug is intentionally unpronounceable to facilitate the use of its brand name in conversation. There is an agreed system to naming biologic drugs,¹ however, apart from the length of their names, a major problem is that they often combine strings of letters that have no equivalent in the English language.² We therefore have no reference points to help us with the pronunciation.

Some may say that such uncertainty around how to pronounce drug names is not a significant problem, especially in the age of electronic prescribing. The problem of lookalike and soundlike drug and brand names is well recognised,¹ but there is an evidence gap regarding any impact that mispronunciation may have on patient safety. There are many instances where verbal communication remains at the core of drug transactions between health professionals and with their patients. Telephone orders between prescribers,³ clinical handovers, voice-recognition software and text-to-speech systems are all situations where misunderstanding could result in the wrong drug being given.^{4,5} The problem is amplified by unfamiliarity when all you have heard is *blah-dee-blah-mab*.

The first time I heard someone say *clippy-DOG-rel* (clopidogrel), I was taken aback. It had never occurred to me to pronounce the drug in this way, but how should Australians say this word?

The pharmaceutical company, which markets a new drug, knows how to talk about its product. The drug has been nursed through clinical trials and given an accepted, non-proprietary name. When the company’s representatives promote the drug they introduce the new name with its preferred pronunciation. However, not everyone gets a visit from a drug company representative and the focus is often on more mellifluous brand names. Sometimes, names end up with a life of their own and before you know it, *klo-PIDD-oh-grell* is *clippy-DOG-rel*.

In 2003, the then National Prescribing Service (NPS) commenced its work on contextualising the role of new drugs on the Pharmaceutical Benefits Scheme with the Rational Assessment of Drugs and Research (RADAR) publication. One of the ideas for RADAR recognised that, as the new drug name would be unfamiliar to health professionals, it would be useful to publish a phonetic spelling of the generic drug name to aid pronunciation. This dovetailed with other NPS messages, directed to consumers, that they be familiar with the generic name of their medicines and not just the brand names.

What seemed an unambitious goal – to source pronunciations of drug names – turned out to be particularly difficult. Australian product information never includes a pronunciation guide. While Consumer Medicines Information (CMI) does include pronunciation tips occasionally, the coverage is extremely patchy and, surprisingly, there can be inconsistencies. The CMI for Iscover suggests that clopidogrel is pronounced *klo-PIDD-oh-grell*, while the CMI for DuoCover suggests *clop-id-o(h)-grel*. Both products are marketed in Australia by the same company.

As with most things, the Internet will give you all the variation that might exist on a topic and is therefore of limited reliability. For example, more than one website suggested the cholesterol-lowering drug, ezetimibe, be pronounced *e-zet-e-mib*, with a short suffix that could easily be confused with the biologic drug suffix *ib*.

In the end, RADAR was able to use the American Medical Association’s Dictionary of United States Adopted Names (<https://www.ama-assn.org/about-us/adopted-names>) as a starting point for how the drug might be pronounced. However, the pronunciation requires a familiarity with the arcane use of diacritical marks, and thus needs to be used in conjunction with a key to pronunciation (<https://www.ama-assn.org/pronunciation-guide>).

The question is – can we rely on North American interpretations when Australian speech patterns are so very different? A case in point is dabigatran. A recent US commentary asserted the drug is pronounced *da bye gat’ ran*.² The long ‘i’ immediately attracted my attention as being a regional difference unlikely to be repeated in Australia: think *sem-eye final* (semi-final) or *ant-eye-bye-o-tic* (antibiotic).

So what can we do? Free online sources such as Drugs.com (https://www.drugs.com/drug_information.html) and ClinCalc.com (<http://clincalc.com/pronouncetop200drugs>) provide pronunciation examples, notwithstanding the North American accents. Other sources are available, but sit behind paywalls.

At a local level, in the same way there was a move to include the active ingredient as prominently as the brand name on labelling, perhaps a groundswell could begin to systematically include phonetic pronunciation of the generic drug name in the CMI. Additionally, just

as the product information and CMI for a drug can be found on the website of the Therapeutic Goods Administration, perhaps an audio file with the correct pronunciation could be included. This audio file should be a human spoken voice, not a digitised voice typical of text-to-speech systems.

These easily achievable solutions could mitigate the problem immortalised by the Gershwins and have us all singing from the same song sheet. ◀

Craig Patterson is a former editor of NPS RADAR.

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Letters to the Editor

Neuropathic pain – definition and drug therapy

Aust Prescr 2018;41:178–9

<https://doi.org/10.18773/austprescr.2018.069>

I thank Dr Murnion for her timely update regarding the definition and treatment of neuropathic pain.¹

Despite the rewording, the new definition by the International Association for the Study of Pain (IASP) may still be over-inclusive by attempting to encompass a heterogeneous constellation of syndromes and conditions with poorly understood pathophysiology.² This has significant ramifications and causes confusion over the pharmaceutical management of neuropathic pain. For example, while gabapentinoids can be beneficial for postherpetic neuralgia and diabetic neuropathy, they do not appear to be better than placebo in sciatica,^{3,4} yet all these conditions are called neuropathic pain under IASP terminology.

The IASP recommended duloxetine, tricyclic antidepressants, pregabalin and gabapentin as first-line drugs.⁵ However, Australian guidelines still recommend amitriptyline first-line, pregabalin and gabapentin second-line, and duloxetine as a second- or third-line consideration.⁶

These differences are important in clinical practice. Amitriptyline and duloxetine are not subsidised by the Pharmaceutical Benefits Scheme (PBS) for neuropathic indications. Pregabalin and gabapentin are only PBS-subsidised when prescribed for refractory neuropathic pain unable to be controlled by other drugs. It is unclear what the 'other drugs' are, although for pregabalin, the Pharmaceutical Benefits Advisory Committee (PBAC) approval documents for neuropathic pain suggest these drugs may include amitriptyline and gabapentin.⁷ Nevertheless, PBS subsidy for both gabapentinoids is not for first-line drug therapy. The fact that these two drugs are the only PBS-subsidised drugs for neuropathic pain with poorly defined criteria may inadvertently result in a lower threshold for prescribing them.

After PBS listing there was greater than expected use of pregabalin for neuropathic pain and a higher than expected discontinuation rate after the first prescription. A subcommittee of PBAC concluded:

'Prescribing of pregabalin in clinical practice may not be optimal. A large number of patients do not have the dose of pregabalin up-titrated and persistence to therapy is poor.'⁸

Some of this prescribing could be related to attempts to use pregabalin for treating sciatica as neuropathic pain.

There are increasing concerns gabapentinoids are being misused.^{9,10} The UK has restricted them as Class C controlled drugs effective from April 2019.¹¹ Pregabalin appears to be highly lucrative in the Australian market leading to attempts at an early application for PBS listing before patent expiry (and associated legal proceedings).¹² Given the lack of efficacy of gabapentinoids in certain conditions still classified as neuropathic pain, I urge a review of prescribing indications and careful rewording of PBS-authority requirements.

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Bridin Murnion, the author of the article, comments:

 The definition of neuropathic pain used in the article is the current internationally agreed definition.¹ This is refined from previous definitions, and, with the planned reclassification of chronic pain for ICD-11, there will likely be further refinement.²

The most recent meta-analysis identifies that the aetiology of neuropathic pain does not predict the response to drug treatments.³ Clearly, as new, robust evidence emerges, it must be included in the debate and incorporated into clinical practice.

Amitriptyline is on the general schedule of the Pharmaceutical Benefits Scheme (PBS), although neuropathic pain is 'off-label' use. The processes recommended for off-label prescribing, including patient discussion and agreement, provide a framework for its use.⁴

Duloxetine is PBS-subsidised for major depression. If a patient with neuropathic pain does not have concomitant depression, consider the processes for off-label use, including a discussion of cost.⁴

There is increasing concern about gabapentinoid misuse.⁵ It is timely, therefore, to consider how to improve prescribing, including scheduling changes and improved diagnosis of neuropathic pain and substance use disorder. As many patients do not respond,³ deprescribing pregabalin and gabapentin when they are not effective is critical. Non-pharmacological strategies must also be a major component of any pain management plan.⁶

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ARTICLE

Home detox – supporting patients to overcome alcohol addiction

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Sydney Doctors, Sydney**Keywords**alcoholism, alcohol
withdrawal, detoxification*Aust Prescr* 2018;41:180–2<https://doi.org/10.18773/austprescr.2018.059>**SUMMARY**

Helping a patient through home alcohol detoxification has high patient satisfaction rates and is hugely rewarding for the GP.

The majority of dependent drinkers can detox safely and successfully at home and do not require hospital admission.

Daily review by a GP or nurse is important for at least the first four days.

Prescribing acamprosate, naltrexone or disulfiram is advised to maintain abstinence after detox but should only be used with ongoing support.

Ongoing psychosocial support is essential for recovery.

Introduction

Alcohol is the most dangerous addictive drug in the world and kills 15 Australians every day.¹ The harms related to alcohol dependence are undisputed, yet discussing alcohol consumption with patients still seems to be a difficult conversation.^{2,3} One could argue that, as well as alcohol's cultural acceptability, this is partly due to the lack of options in primary care for treating alcohol dependency.

Patients with alcohol dependency are often referred to over-burdened tertiary services, or are given a potentially dangerous prescription of diazepam without the support required for a safe detox process.⁴ GPs are well placed to offer a structured home alcohol detox service for their patients.

Home detox is the process of safely withdrawing a dependent drinker from alcohol without admission to an inpatient unit. A recent systematic review⁵ of 20 studies found that community detoxification was safe with high completion rates. It proved that detox in the community, as compared to an inpatient unit, had better drinking outcomes, good acceptability and was between 10.6 and 22.7 times cheaper.

It is often difficult for a patient to ask for help due to the cultural stigma around being branded an 'alcoholic'. A non-judgemental approach and the use of motivational interviewing techniques are essential. Once you have built rapport, a thorough assessment can be undertaken.

There is evidence that home detox is ideal for minority communities such as Aboriginal and Torres Strait Islander people.⁶ This may be extrapolated to culturally and linguistically diverse populations.

How to do a home detox

At the first appointment, it is recommended that you obtain some baseline observations and blood tests. This should include full blood count, urea and electrolytes, liver function, iron studies, glucose, calcium, magnesium and phosphate. Screen patients with the following questionnaires:

- Alcohol Use Disorders Identification Test (<https://patient.info/doctor/alcohol-use-disorders-identification-test-audit>)
- Severity of Alcohol Dependence Questionnaire (<http://php.nhs.uk/wp-content/uploads/sites/26/2013/11/SADQ.pdf>)
- Kessler Psychological Distress Scale (https://www.tac.vic.gov.au/files-to-move/media/upload/k10_english.pdf).

To save time, the patient can take these questionnaires home and bring them back to their follow-up appointment.

If you are considering a medicated detox, guidelines suggest starting the patient on oral thiamine 200 mg for two weeks before starting the detox.⁷ Intramuscular injections of thiamine are also beneficial, although these are expensive for the patient (approximately \$100). This reduces the risk of Wernicke's encephalopathy. For low-risk continuing drinkers 100 mg thiamine daily is generally enough.

Diazepam can be used in a weaning regimen (Table) over several days to reduce the risk of seizures and withdrawal syndrome and to ease alcohol cravings.⁸ Oxazepam is a safer alternative if the patient has concurrent liver impairment, as it does not require hepatic oxidation.

Table Possible diazepam regimen for home detox based on severity of alcohol dependence *8

	Mild	Moderate	Severe	Complicated
Daily standard drinks	10–14	15–25	30–40	>50
SADQ score	<16	16–30	>30	>30 plus medical problems
Setting	Home	Home	Inpatient services	Inpatient services
Suggested prescribing regimen – diazepam				
Day 1	Symptomatic – 5 mg 4 times a day and 5 mg when required	10 mg 4 times a day and 10 mg when required		
Day 2	5 mg 3 times a day	5 mg 4 times a day		
Day 3	5 mg twice a day	5 mg 3 times a day		
Day 4	5 mg at night	5 mg twice a day		
Day 5	5 mg at night	5 mg at night		
Day 6		5 mg at night		

* As prescribed by the author SADQ Severity of Alcohol Dependence Questionnaire

Encourage patients to keep drink diaries either on paper or on an alcohol tracker phone app (such as AlcoDroid Alcohol Tracker). This not only increases their awareness of how much they are drinking, but also their feelings around their intake. Patients should also be encouraged to access resources at this early stage as it may help them to become more mindful, and to decrease their reliance on alcohol as a coping mechanism. Useful resources include online alcohol counselling and resources at www.ontrack.org.au, the Daybreak phone app, and This Naked Mind book and blog by Annie Grace (<https://thisnakedmind.com/blog>).

What precautions are needed for a safe detox?

There are several contraindications to home detox. These include:

- not having access to a support person and safe housing for the first few days
- a history of withdrawal seizures or delirium
- problematic drug use
- suicidality
- serious illness.

A signed patient contract is helpful to set clear boundaries (see Box). Important inclusions are consenting to a urine drug screen on day one, a daily breathalyser test, a scheduled GP review, an agreement that they will not drink or drive while taking benzodiazepines, and an intention to comply with an aftercare program.

Box Example of a patient contract for alcohol detoxification

CONTRACT

1. I understand that I must not drive while taking diazepam or during alcohol detoxification.
2. I agree to undertake a urine drug screen before undertaking detox.
3. I understand that the practice has a zero tolerance to the consumption of alcohol during detox. Consuming alcohol while receiving treatment would result in discharge from the detox program.
4. I agree to attend daily while undergoing detoxification.
5. I understand that I will be breathalysed daily before being given medication. The reading needs to be 0, otherwise medication will not be prescribed.
6. I agree to have blood tests at 1 month and 3 months after completion of my detoxification.
7. I accept that I must attend aftercare such as Alcoholics Anonymous, SMART Recovery or be under the care of a psychologist, having completed my detoxification.
8. I understand and accept that the practice has a ZERO tolerance to aggression and harassment. This would result in immediate discharge.

Signed:

Client: Date:

Doctor Date:

Nurse Date:

ARTICLE

Home detox – supporting patients to overcome alcohol addiction

During home detox, in addition to breathalyser tests, daily assessment should include the patient's pulse, temperature and blood pressure. The revised Clinical Institute Withdrawal Assessment can also be used.⁹

What non-drug strategies are there to help withdrawal?

During the detox, it is important to eat small and frequent meals if possible. Protein-rich foods such as fish, dairy products and vegetables are important along with thiamine and a multivitamin. Plenty of fluids including sweet drinks such as tea or decaffeinated coffee should be encouraged to prevent hypoglycaemia, as well as lots of water. Melatonin can be used for sleep disturbance. Give patients the Alcohol and Drug Information Service (ADIS) telephone number (1800 422 599) in case they need support or advice when the surgery is closed.

What are the common pitfalls with home detox?

Patients are often very keen to start the detox on the same day they visit their doctor. However, planning is essential and those who rush into it, or go 'cold turkey' themselves, are at much higher risk of a withdrawal syndrome and relapse. It is important to build a relationship with your local addiction specialists because having a good pathway into inpatient care is necessary for high-risk patients.

Is home detox suitable for other drugs of dependence?

This approach is not designed for other drugs. There is no monitoring system, such as the breathalyser, for other drugs and each one requires a different strategy. Benzodiazepine dependence, for example, needs a weaning schedule over many weeks with regular review and psychological support.

What ongoing support is available?

Following detox, a structured aftercare program is essential for long-term recovery and for patients to achieve their agreed drinking goals. Aftercare can include GP review, alcohol counselling, cognitive behavioural therapy, exercise physiology, dietetics, group support such as Alcoholics Anonymous and SMART Recovery, and phone apps such as a sobriety counter. Health Pathways and ADIS are excellent GP resources. Naltrexone and acamprosate are both available via the Pharmaceutical Benefits Scheme for relapse prevention. Disulfiram, which is not subsidised, is also available but it should be started with a period of supervised administration as it can be dangerous if the patient drinks alcohol. Disulfiram may however be useful for highly motivated individuals.

Conclusion

Supporting patients through home detox is proven to be safe, successful and cost-effective. The patient-centred, confidential and discreet location of general practice makes it extremely accessible and provides a safe and non-judgemental environment. ◀

Conflict of interest: none declared

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FURTHER READING

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Perimenopausal depression – an under-recognised entity

SUMMARY

There is a high rate of suicide in women aged 45–54 years. This may be related to the biological changes associated with the menopause.

Perimenopausal depression may present with symptoms that differ from those of typical depression.

Management can include psychotherapy and other non-drug interventions. If drug treatment is indicated, it may be hormone replacement therapy, an antidepressant or both.

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Keywords

antidepressants, hormone replacement therapy, menopause

Introduction

Mental health disorders can have devastating impacts on women as they approach menopause. This phase of a woman's life, typically between 42 and 52 years of age, is known as the 'perimenopause' and mental illness is very prevalent, in women at this stage. The risk of serious depression is significantly increased in perimenopausal women.¹ The adverse impact also affects her family and society.

Research specifically targeting the mental health of perimenopausal women is lacking. There is a gap in the recognition and provision of appropriate treatments for middle-aged women experiencing depression related to the hormonal changes of the menopause.

Epidemiology

Australian statistical data² show that the highest age-specific suicide rate for females in 2015 was in the 45–49 age group with 82 deaths (10.4 per 100 000). The second highest rate of suicide was in women aged between 50 and 54 years. These suicides should alert us to think about contributing factors, including biological changes in the gonadal hormones associated with the transition to menopause as well as social and psychological stresses in the midlife period.

In the 2007 National Survey of Mental Health and Wellbeing, the Australian Bureau of Statistics identified that 43% of women aged 18–65 years had a mental health problem at some point in their lives. In the preceding year, twice as many women compared to men suffered from mood disorders and four times more women experienced anxiety disorders. Among those with a mental illness in the preceding year, women had higher rates of suicidal thoughts and plans, compared to men. This shows that women clearly carry a high burden of mental illness and suicidality.

The Australian Bureau of Statistics has estimated that the economic cost of depression and anxiety in women (from lost productivity) could be as high as \$22 billion per year. As outlined in an Australian Health Policy Collaboration Paper,³ current funding for mental health from the Australian Government was 'neither effective nor efficient'. The paper highlighted that 'the lack of a gender lens, leading to gender-blind data and gender-blind proposals for reform, is problematic'. Furthermore, the social and psychological costs of depression and anxiety in women are extraordinarily high, when one considers the impact on families, communities and workplaces where women have vital roles. In addition to their many roles in the workforce, women commonly provide much needed care for children, partners and parents.

Diagnostic difficulties

The World Health Organization defines the perimenopause as 'the time immediately preceding the menopause, beginning with endocrine, biologic and clinical changes, and ending a year after the final menstrual period'. The diagnosis of perimenopausal depression is therefore often made retrospectively. To complicate matters the physical symptoms of the menopause often present much later (up to five years) than the psychological symptoms. This delay can make the diagnosis of perimenopausal depression very difficult. It is important for health professionals to consider whether women who experience depressive and anxiety symptoms for the first time in their mid-40s are actually experiencing depression related to the perimenopausal hormone fluctuations. Similarly, women who experience an exacerbation of a previously well-controlled depression may also be experiencing a perimenopausal relapse.

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Symptoms

Perimenopausal depression includes a wide range of symptoms. Some are seen in the 'typical depression' that men and younger women experience, while other symptoms are unusual. Perimenopausal symptoms can fluctuate in severity, thus adding to the diagnostic difficulty. The common symptoms in perimenopausal depression (see Box) are detailed in a questionnaire called the MENO-D.⁴ In particular, the cognitive symptoms, paranoia and irritability are marked in perimenopausal depression compared to symptoms of major depressive disorders seen in men or younger women.

Management of perimenopausal depression

The course of mental illness in women differs from that of men and is greatly influenced by biological, psychological and social changes over the life cycle. However, most treatments for mental illnesses have been developed and trialled in the 'typical' male patient which may not be the optimal treatment for women with mental ill health related to the menopause.

It is vital to investigate the physical health of a woman presenting with perimenopausal depression to rule out other causes for her symptoms, such as thyroid disorders and autoimmune disorders. This also establishes a good physical baseline for the woman as she embarks on menopausal changes and possibly hormone treatments. Having ruled out other causes of the symptoms, the treatment of perimenopausal depression needs to take a holistic biopsychosocial approach.

Psychosocial treatments

If the woman's perimenopausal depression is clearly related to work or relationship problems, then psychotherapy is an important intervention. Other useful interventions for general well-being include

education about menopause, regular exercise, mindfulness techniques, yoga and dietary advice. Minimising alcohol intake is very important for the patient's mental and physical health.

Drug or 'biological' treatments

Treatments for perimenopausal depression usually include antidepressants and gonadal hormones. Often, the order in which they are used depends on the clinician's particular expertise or medical speciality. Hormone therapy alone may be appropriate for recent onset depression, without suicidality, in otherwise healthy women experiencing other perimenopausal symptoms. The hormone therapy chosen must be tailored for each patient. Recommendations by the International Menopause Society, updated in 2016,⁵ are a useful, comprehensive set of evidence-based practice guidelines.

Tibolone is a synthetic steroid with a mixed hormonal profile which has shown benefit in treating perimenopausal depression.⁶ Tibolone can cause minor intermenstrual bleeding, but does not cause increased breast density.⁶

Bioidentical hormones are compounds synthesised to resemble ovarian hormones. There are limited safety and dosing data on these compounds which are not recommended by the International Menopause Society.⁵

Antidepressant treatment for perimenopausal depression usually begins with a selective serotonin reuptake inhibitor. If this approach is not effective, serotonin noradrenaline reuptake inhibitors are often second-line drugs. However, both classes can have agitating adverse effects and a woman with prominent perimenopausal insomnia, irritability and anxiety may experience exacerbation of these symptoms with drugs such as fluoxetine. Agomelatine is a newer antidepressant with positive sedative impact and fewer adverse effects in women with perimenopausal depression.⁷

Combining hormone therapy and antidepressant therapy may be required for perimenopausal women with depressive symptoms that do not respond to either treatment alone. In such cases, the adverse effects of combined treatment need to be monitored carefully.

Box Symptoms of perimenopausal depression

- Low energy
- Paranoid thinking
- Irritability or hostility
- Decreased self-esteem
- Isolation
- Anxiety
- Somatic symptoms
- Sleep disturbance
- Weight gain
- Decreased sexual interest
- Problems with memory and concentration

Conclusion

Most women with perimenopausal depression respond to treatment. It is important to recognise the special symptoms of perimenopausal depression as well as the serious nature of this depression. Clinicians need to provide a tailored management approach for these women. It is not appropriate to deem this

type of depression as minor or presume that, once the hormonal fluctuations settle, the depression will improve. The process of menopause can take many years, during which the patient's quality of life and that of her family, may deteriorate irreparably. Tragically, suicide in middle-aged women is becoming a more common occurrence. ◀

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ARTICLE

Insulin pumps in general practice

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Melbourne**Keywords**diabetes, glucose, insulin,
insulin infusion systems,
ketoacidosis*Aust Prescr* 2018;41:186–90<https://doi.org/10.18773/austprescr.2018.056>**SUMMARY**

Insulin pumps deliver continuous subcutaneous rapid-acting insulin in a flexible manner. In Australia their main use is in the management of type 1 diabetes.

The care of patients with type 1 diabetes on an insulin pump should involve a team approach which includes the GP as well as specialists in diabetes. The GP should therefore understand the terminology associated with insulin pump therapy. Technical support is available from the manufacturer's helpline.

If blood glucose is significantly elevated or the patient is nauseated, blood ketones should be checked. When ketones are elevated the insulin delivery line should be changed, and referral to an emergency department may be needed.

Introduction

People with type 1 diabetes have an absolute deficiency in islet cell function which requires therapy with injections of insulin. Despite advances in injection equipment and modern insulin formulations with favourable pharmacokinetic profiles, there remain limitations in the flexibility and responsiveness of injected insulin. For example, there is very little opportunity to influence basal insulin delivery after an injection of long-acting insulin. Some patients (for example those who have completed courses such as Dose Adjustment for Normal Eating) can make appropriate adjustments to their dose of rapid-acting insulin. However, adjustments are usually constrained by the increments in the dose of insulin that are able to be administered and the patient's ability to perform calculations to account for meals and to correct for glucose concentrations outside a healthy range. These constraints are particularly apparent in people with type 1 diabetes as insulin requirements can vary significantly and rapidly. Insulin pumps have been developed to address these shortcomings.

In Australia insulin pumps are almost entirely used for the management of people with type 1 diabetes. In the USA, in addition to those with type 1 diabetes, there are a significant number of people with type 2 diabetes who use insulin pumps.

Insulin pumps

Since the commercialisation of the first subcutaneous insulin pumps in the 1970s, pump therapy has changed dramatically. It has evolved from large bulky devices that could only deliver a single basal rate and required patients to calculate bolus doses, to today's pager-sized devices with

increasingly sophisticated technology. Insulin pump therapy is rapidly becoming the standard of care for the management of type 1 diabetes.

Insulin pumps vary in size and appearance depending on the model, but the basic set-up is common to most models. The pump houses an insulin cartridge or 'reservoir'. This reservoir is connected to an insulin delivery line which in turn is connected to a subcutaneous cannula that delivers insulin to the patient (Fig. 1). The reservoir, delivery line and cannula generally need to be replaced every three days. Just as with injected insulin, the patient should rotate the site for the insertion of the cannula.

Dosing

When commencing insulin pump therapy the amount of rapid-acting insulin to be delivered by the pump is estimated from calculations based on the total daily dose of injected insulin. Usually a 20% reduction in the total daily dose of insulin is estimated as the appropriate total daily dose for pump therapy. Half of this estimate is delivered by the pump to meet basal insulin needs. The initial bolus doses of insulin for meals are estimated using the 'rule of 500' where the number 500 is divided by the total daily injected dose of insulin in units to give an insulin-to-carbohydrate ratio.

The four main settings that need to be programmed into an insulin pump are:

- basal dosing (basal rates)
- bolus dosing (insulin-to-carbohydrate ratio)
- blood glucose correction settings (insulin sensitivity factor also known as the correction factor)
- insulin action time.

The pump only holds and delivers rapid-acting insulin, so basal dosing is given as an hourly rate. For example, 24 units daily of a long-acting insulin would be equivalent to one unit per hour of rapid-acting insulin as a continuous infusion. Basal dosing via an insulin pump is much more flexible than long-acting insulin injections because different basal rates can be given at different times of the day. Most pump wearers have between one and six different basal rates over 24 hours.

Current generation insulin pumps do not automatically administer insulin boluses. Bolus administration is initiated by the patient. The bolus doses of rapid-acting insulin delivered by a pump's bolus calculator may have two components. The first represents an amount of insulin calculated to address the glucose influx associated with a meal. This dose is calculated with the pump's insulin-to-carbohydrate ratio.

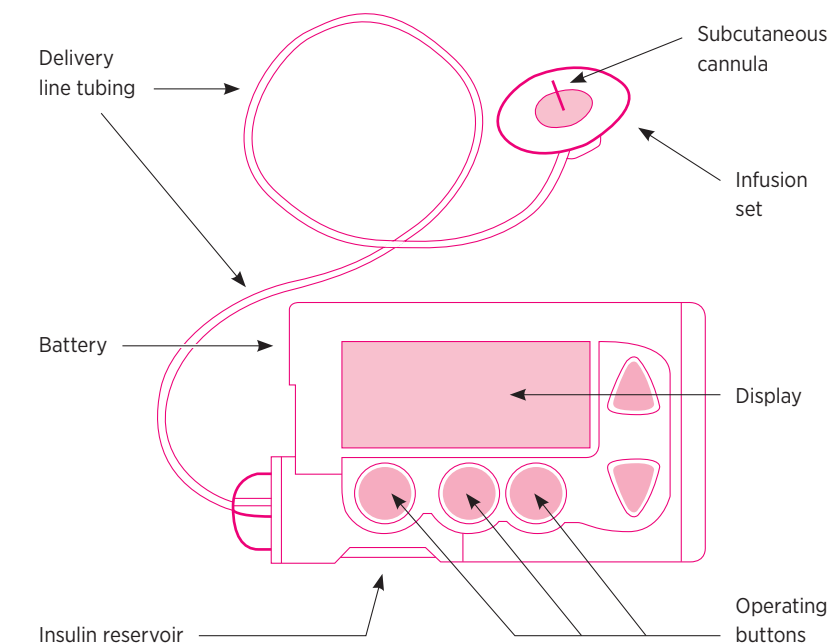
For meals, the pump delivers one unit of insulin for every specified amount of carbohydrates. For example, for a meal containing 20 g carbohydrate with an insulin-to-carbohydrate ratio of 1 unit of insulin/10 g carbohydrate, the pump would deliver 2 units of insulin. When adjusting the insulin-to-carbohydrate ratio it should be noted that a decrease in the number of grams of carbohydrate per unit of insulin results in an increase in insulin dose. For example, a change from 1 unit of insulin/15 g carbohydrate to 1 unit of insulin/10 g carbohydrate increases the amount of insulin delivered by one third.

When the person's blood glucose is in the target range no additional insulin is administered with the bolus. If the glucose is elevated, the pump's bolus calculator may administer a second component to the bolus to bring the concentration down into the target range. This additional dose of insulin is based on the insulin sensitivity factor. If the person is not eating and the glucose concentration is above the target range, a bolus of rapid-acting insulin may be delivered purely to correct the elevated glucose.

Bolus doses of insulin for corrections are calculated automatically by the insulin pump using the patient's finger-prick glucose (entered via a compatible blood glucose meter) and the pre-programmed insulin sensitivity factor. This factor is the amount that blood glucose (mmol/L) is lowered by one unit of insulin. For example, for an entered blood glucose of 7 mmol/L and a pre-set target blood glucose of 5 mmol/L, an insulin sensitivity factor of 2 mmol/unit would result in the delivery of 1 unit of insulin.

Insulin action time refers to an estimate of the duration of the activity of the insulin that has already been delivered by the pump subcutaneously. It provides an estimate of the residual activity of rapid-acting insulin delivered by a previous bolus thereby

Fig. 1 Components of an insulin pump



modulating the subsequent delivery of further boluses of insulin. This modulation is aimed at reducing the risk of hypoglycaemia by avoiding the 'stacking' of insulin with multiple boluses.

Monitoring

Continuous glucose monitors are an increasingly popular adjunct to insulin pump therapy (Fig. 2). They allow for real-time monitoring of glucose concentrations via a small subcutaneous electrode or sensor. The sensor measures glucose in the subcutaneous interstitial fluid and sends this information directly to the pump (or a handheld receiver) every five minutes. More recent advances in technology have allowed for insulin pumps to automatically shut off insulin delivery for two hours in the event of hypoglycaemia ('low-glucose suspend') or predicted hypoglycaemia ('predictive low-glucose suspend').

Benefits of pump therapy

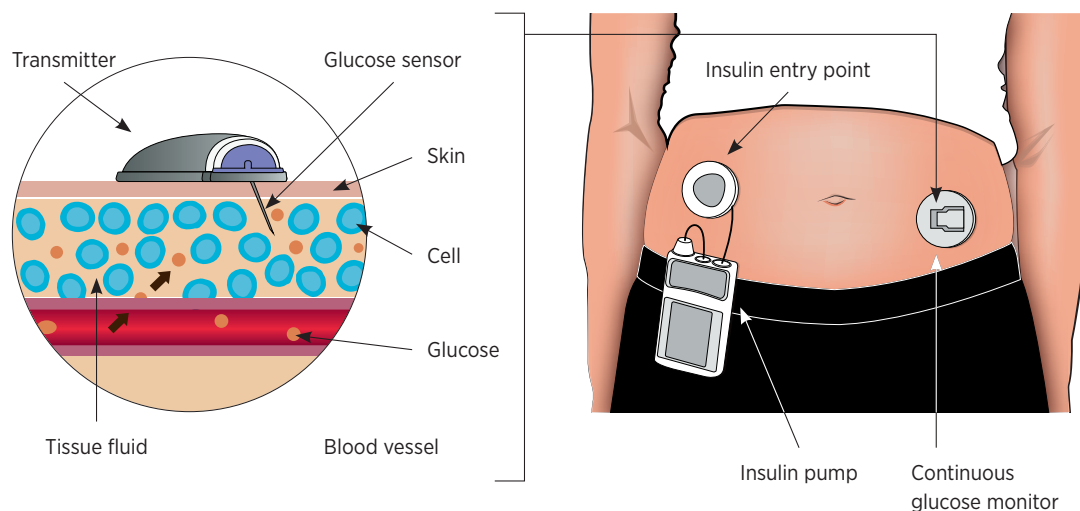
Unlike insulin pens or injections, data can be uploaded from most insulin pumps via web-based software. The data relating to glucose concentrations and insulin delivery can be reviewed by the health professional in conjunction with the patient. The GP should instruct the patient to download PDFs of these reports and bring them to their appointment.

Meta-analyses and randomised controlled trials have reported improvements in glycaemic control using insulin pump therapy compared to multiple

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Fig. 2 Continuous glucose monitoring



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daily injections.¹ These include reductions in blood glucose, reduced hypoglycaemia (both frequency and severity), lower glycated haemoglobin (HbA1c), lower insulin requirements, and improved quality of life. The greatest motivating factor for Australians with type 1 diabetes to use an insulin pump is to improve their diabetes control.²

There are numerous benefits in using insulin pump therapy rather than multiple daily injections. However, it is important to recognise that there may also be some disadvantages (Box).

Box Advantages and disadvantages of insulin pumps

Advantages

- Provides insulin delivery that better mimics normal pancreatic function
- Uses rapid-acting insulin only and minimises glucose peaks and absorption-related variability
- Built-in bolus algorithms to suggest bolus doses based on user-estimated carbohydrate content and blood glucose
- Increased flexibility with day-to-day activities e.g. exercise, mealtimes, travel, shift work
- Can be integrated with continuous glucose monitoring to provide real-time glucose information
- Potential for advanced features e.g. low-glucose suspend, predictive low-glucose suspend

Disadvantages

- External device attached to the body 24 hours a day
- Potential for mechanical malfunction such as blockage or kinking in the infusion set which can lead to diabetic ketoacidosis
- Potential for insertion site problems such as skin infections or local irritation
- High cost and limited access for uninsured patients
- Patients have to be willing and able to manage the technology

Suitability for pump therapy

Careful consideration is essential to determine which patients are suitable for insulin pump therapy. Patients need to be willing and able to self-manage the technology which requires programming by the user. The patient also needs adequate carbohydrate counting skills, and to be competent at blood glucose self-monitoring. They must be motivated to accept responsibility for their own care.

Insulin pumps are typically recommended for patients with suboptimal glycaemic control despite multiple daily injections. In particular, those with frequent or unpredictable hypoglycaemia associated with hypoglycaemia unawareness may benefit. Women planning pregnancy often transition to pump therapy before conception to achieve tighter glycaemic targets pre-pregnancy and to maintain control during pregnancy. Insulin pumps may also provide greater flexibility for people who do shift work, frequent travel, intensive exercise and physical activity.

Access to insulin pumps

In Australia, insulin pump therapy is limited to people with type 1 diabetes who have private health insurance. There are some government subsidy programs and charitable organisations, such as the Juvenile Diabetes Research Foundation (JDRF), that may assist with the cost of an insulin pump in special circumstances. Patients without private health insurance have to purchase the insulin pump themselves. The current commercial price of an insulin pump is approximately \$10 000.

In 2017 a government subsidy for continuous glucose monitors was implemented for people under the age of 21 years. However, patients over 21 years receive no subsidy and must purchase continuous glucose monitors at the full price of approximately \$300–400 per month. Additional costs with pump use include consumables such as infusion sets and reservoirs, costing \$25–30 per month.

Managing insulin pumps in general practice

The management of a patient on an insulin pump requires the involvement of a specialist diabetes team including an endocrinologist, diabetes nurse educator and dietitian. The GP is an essential member of this team and it is therefore important GPs understand the terminology related to insulin pump therapy (Table).³

As a rule, the GP is not routinely involved in altering the pump settings but changes to insulin delivery may be performed in partnership with the specialist team. The GP is not expected to know all things about all pumps and the patient should be able to guide the doctor through the 'button pushing'. In general, the basal insulin delivery determines overnight and pre-meal glucose concentrations, while bolus insulin determines post-prandial glucose levels. Bolus insulin is also used to correct high glucose levels.

It is essential that the patient has prescriptions for rapid-acting insulin for their pump. In addition, they

require pens and needles as a backup for injections of rapid- and long-acting insulin, should the pump fail or should they need to temporarily discontinue insulin pump therapy (e.g. while white water rafting). While the pump is disconnected and suspended during swimming and bathing, alternate means of insulin delivery are usually not required as these activities are usually of limited duration. Nevertheless, it is important that the patient reconnect the pump and cancel the suspension of insulin delivery after their activity. This is important because insulin pumps only deliver rapid-acting insulin. After 4–6 hours of a pump being disconnected insulin activity will fall to zero with a risk of ketoacidosis. If the pump is not able to be reconnected, insulin will need to be given by injection. The patient should also have a current glucagon injecting kit and the relevant people, such as family members, should be educated in its use.

Details of the patient's insulin pump settings at the time of their most recent consultation should be documented in the patient's general practice record. These details include:

- insulin-to-carbohydrate ratios (which may differ through the day)
- basal insulin delivery settings
- insulin action time
- insulin sensitivity factor
- total daily insulin and the amount given as basal insulin.

Table Insulin pump terminology³

Terminology	Definition	Example
Basal rate	Background delivery of small doses of insulin at programmed rates (measured in units per hour)	1 U/hr delivers 1 unit of insulin every hour
Bolus dose	Discrete and more rapid delivery of insulin for food or blood glucose corrections (measured in units)	5 unit bolus delivers 5 units of insulin quickly
Insulin-to-carbohydrate ratio	Number of grams of carbohydrate that one unit of insulin will cover (measured in grams per unit)	10 g/unit delivers 1 unit for every 10 g carbohydrate
Insulin sensitivity (correction) factor	Amount of blood glucose (mmol/L) that is lowered by one unit of insulin (measured in mmol/L per unit)	Insulin sensitivity factor of 2 mmol/unit implies that 1 unit of insulin lowers the blood glucose by 2 mmol/L
Insulin action time	Time entered into the bolus calculator that insulin is estimated to be active in the body (measured in hours)	Generally programmed anywhere between 3 and 6 hours
Reservoir	Cartridge of insulin housed in the pump	
Cannula	Soft flexible tube or steel needle inserted into subcutaneous tissue through which insulin is delivered into the body	
Tubing or delivery line	Plastic tubing that connects cannula to reservoir	
Infusion set	Includes cannula and tubing	
Continuous glucose monitor	Subcutaneous glucose sensor that measures glucose levels in the subcutaneous fluid every few minutes. These may be integrated with a pump	

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This information is most efficiently obtained by uploading data from the insulin pump and incorporating a copy of the report in the patient's record. The data can be uploaded using web-based software to which the patient should have access, or directly from the screen on the pump.

A patient using an insulin pump may consult their GP while unwell and knowledge of the principles of sick-day management is important. As with the patient on multiple daily injections, those with type 1 diabetes should monitor their glucose and ketones closely. A temporary modification of usual basal insulin delivery (also known as a temporary basal rate) may be required on sick days. An increment in insulin delivery is usually required to deal with a rise in stress hormones increasing insulin resistance, but sometimes a reduction may be required if there is an associated diminished oral intake.

Sometimes an unexplained high glucose may be observed which is not explained by a pump malfunction. It is essential that blood ketones are checked. If moderately elevated (>0.4 mmol/L), a corrective dose of rapid-acting insulin should be administered by injection as soon as possible. The insulin delivery line should then be changed and insulin delivery by the pump recommenced. If the ketones are critically elevated (>1.6 mmol/L) or the patient is nauseated and vomiting, they should be sent to an emergency department. Otherwise, the patient should check glucose and ketones hourly and further management should be determined in conjunction with a diabetes specialist team.

Occasionally there is a technical problem and the pump manufacturer's helpline should be contacted for assistance. When it is not safe for the patient to use the pump, and ketosis is not present, the patient will need to revert to multiple daily insulin injections until a replacement pump is available. The dosing for the multiple daily injections in these circumstances should be determined with the specialist team. If specialist advice is not available, the dose of insulin to be injected may need to be provided by the GP, as a temporary measure. As a rule, the average total basal insulin can be injected as long-acting insulin either once daily or preferably divided into two doses. Mealtime rapid-acting insulin doses can be estimated

by using the patient's insulin-to-carbohydrate ratio and, if their glucose concentrations are high, by using their insulin sensitivity factor. However, insulin requirements for pump therapy are usually 20–25% less than with multiple daily injections and therefore this approach may underestimate insulin requirements, but it should be sufficient to avoid ketosis.

Travelling with an insulin pump

While travelling, an accompanying letter on practice letterhead should be provided stating the medical history of the patient, including the diagnosis of type 1 diabetes, and that management is via an insulin pump. A list of current drugs, with generic names and doses, should be included. The letter should stress that it is important that the patient's drugs accompany them, and that the insulin pump should not be disconnected. In particular, the pump should not be put through airport X-ray machines.

Prescriptions should be obtained for insulin and other drugs before travel. In case of pump failure both rapid-acting and long-acting insulin should be obtained along with injecting devices and needles. Sufficient equipment for glucose testing should be packed in the hand luggage. In addition to drugs and glucose-testing equipment adequate quantities of consumables (batteries, insulin reservoirs, insulin delivery sets and sensors for continuous glucose monitoring) should be packed. As a rule, pack twice as many sets as potentially required for the planned period away from home. An adequate supply of consumables should be included in the hand luggage while flying.

Conclusion

Advances in technology have enabled insulin pumps to have a greater role in the management of type 1 diabetes. Successful management requires a team approach. ◀

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SELF-TEST QUESTIONS

True or false?

1. Patients using an insulin pump should change their subcutaneous cannula every three weeks.
2. A patient's daily insulin requirements are usually less when the drug is delivered by an insulin pump rather than injection.

Answers on page 205

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Altering dosage forms for older adults

SUMMARY

Swallowing difficulties in older adults present challenges for medication management, particularly as polypharmacy is so common.

It is also important to review the patient's swallowing difficulties and medication management regularly. The limited availability of oral liquids and other dosage forms given by alternative routes means that crushing tablets and emptying capsules is common practice.

Altering dosage forms can have adverse clinical consequences. It is important to consider whether the medicines are still necessary.

If the medicines are essential, find out if there are alternative formulations. Check guidelines and the product information before altering dosage forms.

The legal implications of altering dosage forms can be minimised by following evidence-based practice, clearly documenting the reason for altering the medicine and obtaining written consent from the patient or their carer. Review the patient's swallowing ability and treatment regimen regularly.

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Introduction

Polypharmacy, dysphagia and age-related pathological changes in older adults present challenges for medication management. As many as one in five older patients has difficulty swallowing and may have problems taking tablets and capsules.^{1,2}

The limited availability of oral liquids, patches and suppositories means that crushing tablets and emptying powder from capsules is very common, particularly in aged-care facilities and nursing homes.^{3–6} Multiple medicines are often crushed together and mixed with a food or a thickening agent for administration.³ Altering solid dosage forms is associated with a number of problems.

The stability and bioavailability of drugs can be significantly changed by the simple act of crushing a tablet, preparing an oral liquid from a tablet or capsule, or mixing a crushed tablet or capsule powder with food or other thickening agents.⁷

Manipulating solid dosage forms remains a significant source of medication error and harm to patients.⁷ It may also result in non-adherence such as missed doses or discontinuation of medicines.^{1,2}

Supporting patients with dysphagia

When faced with a patient who is unable to swallow solid dosage forms, consider the following:⁸

- stopping unnecessary medicines
- finding an alternative commercially available dosage form, for example liquid dosage form
- checking if another drug in the same class is available in a different dosage form
- considering extemporaneously compounded medicine – this remains off-label use but is produced using an evidence-based approach
- trialling medication lubricants
- improving swallowing function with the aid of speech pathologists.

Information on appropriate dosage-form alterations

Often medication errors and unsafe medication use occur when dosage forms are altered because of limitations in health professionals' knowledge and the lack of availability of guidelines or appropriate reference materials.⁶ The Society of Hospital Pharmacists of Australia has produced the Australian Don't Rush to Crush Handbook to assist with appropriate dosage-form modification.⁹ (Similar information is also available as an add-on through MIMS.) The handbook recommends five primary methods of managing a medicine that cannot be swallowed whole.⁹ These include:

- dispersing a suitable tablet or capsule in water
- crushing a suitable tablet
- giving an oral liquid form
- prescribing an alternative medicine
- consulting a compounding pharmacy about the availability of other formulations.

Some examples of suitable alternatives when drugs cannot be modified are described in the Table.⁹ Additionally, there have been significant developments in both transdermal drug delivery and orally disintegrating dosage forms (e.g. olanzapine wafers) which are easily administered to patients with swallowing difficulties.

Bioavailability and stability considerations

Bioavailability represents the amount of drug that reaches the systemic circulation and elicits an effect.⁶ The rate and extent of drug released from the formulation may be altered by the crushing process, resulting in potential changes in the concentration–time profile.⁶ Crushing solid dosage forms may also enhance dissolution and increase bioavailability. For example, if controlled-release opioids are crushed, there is a risk of dose dumping and overdose.⁶

Alternatively, crushing may lower the dose because of drug loss during preparation and administration.^{9–12}

Controlled-release, slow-release and extended-release products are specifically designed to deliver the drug over a prolonged period of time.⁶ If a controlled-release formulation is crushed, the duration of the drug's activity is reduced and the entire quantity of the drug may be immediately released resulting in toxicity.⁶ Crushing enteric-coated medicines that are acid labile will damage the coating and expose the drug to the acidic stomach environment. This may have a two-fold effect of irritating the stomach lining and causing discomfort, or inactivating the drug if it is extremely susceptible to acid degradation.⁹

Mixing formulations with foods and thickeners

Crushed tablets and capsule contents are commonly mixed with food to assist with both drug administration and adherence. In studies of various health facilities, 23–96% of patients were given at least one medicine daily mixed into their food or beverage to mask the unpleasant taste.^{3,5,10} Common foods and beverages used included fruit juices, apple sauce, milk, jams, custards, yoghurt, honey, pudding and in one case sprinkled on a patient's toast.^{5,6,9,13}

Dissolution, which is required before a drug can be absorbed, has been investigated when solid dosage forms were crushed in orange juice, honey, jam, yoghurt and a commercial powder thickener.^{11,12} Although yoghurt is often used as a vehicle for mixing and administering crushed tablets, this is controversial as it may affect drug dissolution.¹² The adhesive properties of honey and jam may not significantly affect dissolution, but they can be sticky in the mouth and their high sugar content can cause dental problems and affect a patient's glycaemic control.¹²

Potential complexation of the drug with the food or an alteration of the pH environment (which can affect drug stability) may also alter a drug's therapeutic effect.⁶ Accurate dosing is also difficult to achieve if patients do not finish their food.¹² Additionally, adding medicines to food and drink may discourage patients from eating.¹⁴

Table **Examples of drugs unsuitable for dosage-form modification and suitable alternatives**⁹

Drug	Suitable alternative
Enteric-coated drugs	
Proton pump inhibitors	Oral granules or dispersible form
Sulfasalazine EN tablets 500 mg	Sulfasalazine tablets 500 mg (plain)
Slow-release/controlled-release drugs	
Metformin 500 mg/1000 mg extended-release tablet	Metformin 500 mg tablet (plain)
Ferrous sulfate 325 mg modified-release tablet	Ferrous sulfate 150 mg/5 mL liquid
Paracetamol 665 mg controlled-release film-coated tablets	Paracetamol 500 mg tablets (plain or dispersible form)
Gliclazide 30 mg/60 mg modified-release tablet	Gliclazide 80 mg tablet (plain)
Dabigatran 75 mg/110 mg/150 mg capsule	No alternative formulation available – consider other anticoagulants

Reference 9 provides a comprehensive list for prescribers to refer to.

Legal implications

Health professionals who modify formulations have both legal and clinical implications to consider (Box). Administration of any medicine that has been altered from the licensed (original) dosage form by any health professional is considered off-label use and has liability consequences.⁹ As modification produces neither an approved or labelled product, administration, particularly if mixed with food or a thickening agent could be seen as unlawful practice.⁷ In some cases dosage-form modification may be occurring without the knowledge or authorisation of the prescriber.²

Potential liability may be minimised by:⁹

- clearly documenting the reason for altering the medicine
- following evidence-based, safe and effective practice
- obtaining written consent from the consumer or legal guardian where possible
- regularly reviewing the swallowing ability of patients and discussing medication management needs.

Conclusion

Older adults make up 20% of the population, but take 50% of all prescribed medicines. Consequently, the bioavailability, stability, safety, clinical and legal impacts of drug administration and alteration require careful consideration.

The following recommendations may be used as a guide if patients are having swallowing difficulties:

- consider appropriate alternative medicines and formulations
- use guidelines, references or product information before authorising medicines to be crushed
- evaluate the patient's ability to swallow dosage forms regularly. ◀

Conflicts of interest: none declared

Box Clinical and legal implications of altering solid dosage forms^{7,9}

Clinical implications (examples)

Increased toxicity (crushing extended-release products results in dose dumping)
Medication errors
Reduced efficacy (crushing enteric-coated tablets may result in the drug being destroyed by stomach acid)
Instability of the drug (pharmacokinetic changes)
Unpalatability (resulting in non-adherence)
Potential risk to healthcare workers (exposure to cytotoxic drugs)
Unintended aspiration (patient with dysphagia aspirating a medicine)
Incorrect dosage administration (loss of drug during crushing process)

Legal and professional implications (examples)

Off-label drug use (opening a capsule or crushing a tablet before administration)
Lack of consent for administration (patient may be unaware of medication provided in food)
Cross contamination (one crushing device being used for multiple patients' medicines, placing patients at risk of adverse effects such as allergic reactions)

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Top 10 drugs 2017–18

Aust Prescr 2018;41:194
<https://doi.org/10.18773/austprescr.2018.067>

Tables 1–3 show the top 10 drugs for the year July 2017 – June 2018. The figures are based on PBS and RPBS prescriptions from the date of supply. The figures include prescriptions under the co-payment (non-subsidised).

None of the most frequently prescribed drugs in Australia appears in the Top 10 drugs by cost. That list is dominated by sofosbuvir and its combinations for the treatment of hepatitis C.

Table 1 Top 10 drugs by DDD/1000 pop/day

Drug	DDD/1000 pop/day*
1. atorvastatin	71.34
2. rosuvastatin	54.02
3. perindopril	51.55
4. amlodipine	46.84
5. irbesartan	33.29
6. candesartan	33.11
7. telmisartan	30.89
8. esomeprazole	29.40
9. ramipril	27.93
10. metformin	24.89

Table 2 Top 10 drugs by prescription counts

Drug	Prescriptions
1. rosuvastatin	11 246 365
2. atorvastatin	10 863 219
3. esomeprazole	9 442 144
4. pantoprazole	7 112 063
5. perindopril	6 466 954
6. cefalexin	5 458 659
7. amoxicillin	5 253 018
8. metformin	5 006 664
9. amoxicillin + clavulanic acid	4 680 931
10. escitalopram	4 187 180

Table 3 Top 10 drugs by cost to government (does not include rebates)

Drug	Cost to government	DDD/1000 pop/day*	Prescriptions
1. sofosbuvir + velpatasvir	\$695 729 924	†	31 079
2. aflibercept	\$324 696 598	†	255 264
3. adalimumab	\$322 733 592	41.48	229 719
4. ledipasvir + sofosbuvir	\$244 917 648	†	10 990
5. ranibizumab	\$218 702 078	†	174 627
6. nivolumab	\$215 410 197	†	43 215
7. sofosbuvir	\$204 520 430	0.99	10 451
8. denosumab	\$189 073 508	44.26	673 160
9. trastuzumab	\$169 958 330	†	55 980
10. pembrolizumab	\$148 956 436	†	17 631

DDD defined daily dose

PBS Pharmaceutical Benefits Scheme

RPBS Repatriation Pharmaceutical Benefits Scheme

* DDD/thousand population/day is a more useful measure of drug utilisation than prescription counts.

It shows how many people in every thousand Australians are taking the standard dose of a drug every day.

DDD includes use in combination products. The calculation is based on ABS 3101.0 – Australian Demographic Statistics for December 2017 (as at March 2018).

† The World Health Organization has not allocated a DDD for this drug.

Source: Department of Health, October 2018. ©Commonwealth of Australia

Medicines Australia Code of Conduct: breaches 2017–18

The Medicines Australia Code of Conduct guides the promotion of prescription products by pharmaceutical companies.¹ Each year Medicines Australia publishes a report, from its Code of Conduct Committee, which details all the complaints that have been received about advertising and other promotional activities.

In 2017–18 there were three complaints made, which were dealt with under the current (18th) edition of

the Code of Conduct.¹ Only one of these was found to breach the Code of Conduct (see Table). More details can be found in the full annual report on the website of Medicines Australia.²

The website of Medicines Australia also provides information about some of the payments made by the industry. These include support for consumer organisations, third party meeting sponsorships, and payments to healthcare professionals.³

Keywords

Medicines Australia, codes of conduct

Aust Prescr 2018;41:195

<https://doi.org.au/10.18773/austprescr.2018.062>

Table Breaches of the Code of conduct July 2017 – June 2018

Company	Brand (generic) name	Material or activity	Sanction
GlaxoSmithKline	Breo Ellipta (fluticasone furoate with vilanterol)	Promotional material	\$100,000 fine, material not to be used again in same or similar form.

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3. Medicines Australia. Transparency reporting. <https://medicinesaustralia.com.au/code-of-conduct/transparency-reporting> [cited 2018 Nov 1]

New drugs

Aust Prescr 2018;41:196–7

<https://doi.org/10.18773/austprescr.2018.064>

First published
18 October 2018

Asfotase alfa

Approved indication: hypophosphatasia

Strensiq (Alexion)

Vials containing 18 mg, 28 mg, 40 mg, 80 mg

Australian Medicines Handbook section 10.3.3

Hypophosphatasia is a rare disorder that causes defective mineralisation of bone. It is caused by genetic mutations which result in reduced activity of (tissue non-specific) alkaline phosphatase. Hypophosphatasia can present in a variety of ways. In children it can cause failure to thrive, short stature, fractures, rickets, muscle weakness and loss of teeth. Renal function can be impaired, but respiratory failure is the main cause of death. There is no effective treatment and the mortality in infants is at least 50%.

Asfotase alfa is a genetically engineered glycoprotein. It has been designed to have enzymatic activity in bone, to address the lack of alkaline phosphatase, with the expectation that mineralisation will improve.

The enzyme has to be given by subcutaneous injection. Doses are determined by the weight of the patient and given three or six times a week. Asfotase alfa is catabolised as a protein and has an elimination half-life of 2.28 days. No studies have been done in children with renal or hepatic impairment.

As hypophosphatasia is a rare disease there are limited numbers of patients to participate in clinical trials. The trials of asfotase alfa have mostly been open-label, phase II studies.

One study enrolled 11 children under three years old with life-threatening hypophosphatasia. After 24 weeks of treatment there was a radiological response in all but one patient. The bony abnormalities continued to improve over 48 weeks. On the 10-point rickets severity scale the median score fell by 8.8 points from a baseline of 9.5 points. At the start of the study 10 children required ventilatory support. Six of the nine patients treated for 48 weeks were able to breathe without ventilatory support.¹

Another study compared the outcomes for 13 children, 6–12 years old, with those of 16 historical controls. Treatment with asfotase alfa resulted in changes on skeletal radiographs after six weeks. This improvement persisted for five years. The rickets

severity score reduced from a median of 2.75 points at baseline to 1 after a year and 0 at five years.

Although not all the children had complete healing, there was no change at all in the historical controls. There were also improvements in physical function and reduced disability.²

When asfotase alfa was approved for use in Australia the safety analysis was based on a total of 71 patients. Some of these patients were adults, but 68 had paediatric-onset hypophosphatasia. Injection site reactions, such as erythema, are very common, so it is important to rotate where the drug is injected. Most patients will develop antibodies to asfotase alfa, but these do not predict who will have a hypersensitivity reaction. Approximately 1% of patients have an anaphylactic reaction. Fever, irritability and headache are very common. With such small numbers of patients it is difficult to be certain if adverse events such as ectopic calcification and craniosynostosis are related to the treatment or the disease. Calcium and parathyroid hormone should be checked during treatment.

Asfotase alfa appears to have some benefit, but hypophosphatasia is a lifelong condition. To assess if the drug has an effect on survival, data from two studies were compared with historical outcomes for patients with perinatal or infantile hypophosphatasia. Compared with 48 historical controls, survival at the age of one year was significantly better (42% vs 95%) in the 37 children given asfotase alfa. At five years the corresponding figures were 27% and 84%.³ As there are limitations in using historical controls, the patients prescribed asfotase alfa will need monitoring to see if the effect of treatment is sustained. If the child lives into adulthood, there are few data to guide whether treatment is effective in patients over 18 years old.

T manufacturer provided some information

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

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

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

NEW DRUGS

Aust Prescr 2018;41:198–9

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18 October 2018

Bezlotoxumab

Approved indication: *Clostridium difficile***Zinplava (Merck Sharp and Dohme)****vials containing 1000 mg/40 mL concentrate****Australian Medicines Handbook section 14**

Infection with *Clostridium difficile* is a potential adverse effect of antibiotic therapy.¹ The *C. difficile* toxins cause diarrhoea and colitis and the infection can be fatal. Some patients develop recurrent infection. While antibiotics are used to treat recurrent *C. difficile* infections, bezlotoxumab may have a role in preventing recurrences.

Bezlotoxumab is a monoclonal antibody. It binds to the B toxin produced by *C. difficile*, thereby neutralising its pro-inflammatory effects. Bezlotoxumab has to be diluted then infused intravenously over an hour. The half-life of the drug is about 19 days, so only a single infusion is needed during a course of antibiotic treatment for *C. difficile*. As bezlotoxumab is an antibody, it is catabolised like other proteins. Renal and hepatic impairment have no effect on clearance and pharmacokinetic drug interactions are unlikely.

The two main placebo-controlled trials of bezlotoxumab involved 2655 adults with primary or recurrent infections with *C. difficile*. These patients were being treated with oral antibiotics and were randomised to continue this standard of care or to receive infusions of bezlotoxumab or actoxumab or both. Actoxumab is another monoclonal antibody (against *C. difficile* toxin A) but it was discontinued after an interim analysis suggested a lack of efficacy. The end point for the two trials was the proportion of patients who had a recurrence within 12 weeks of

being cured by antibiotic therapy. However, a clinical cure (two consecutive days without diarrhoea) was not achieved by all the patients in the trials. In the first trial, 77% of the bezlotoxumab group and 83% of the placebo group had a clinical cure. The corresponding figures in the second trial were 83% and 78%.²

The rate of recurrent infection during the follow-up of both trials was 16.5% in the bezlotoxumab groups and 26.6% in the placebo groups (see Table). Ten patients need to be treated with bezlotoxumab to prevent one recurrent infection. The proportion of patients who had an initial clinical cure and then no recurrence was 64% with bezlotoxumab and 54% with placebo.

Approximately 10% of the patients had a reaction to the infusion of bezlotoxumab, compared with 7.6% of the placebo group. Symptoms include nausea, headache and fever. In the month following the study the frequency of adverse events was similar in both groups. Common complaints were abdominal pain, vomiting and diarrhoea.² Heart failure was more frequent in patients given bezlotoxumab, particularly when there was a history of congestive heart failure. In patients with such a history, 19.5% (23/118) of those given bezlotoxumab died compared with 12.5% (13/104) in the placebo group.

While the rate of recurrence of infection is 10% less in patients given bezlotoxumab, rather than placebo, there is some uncertainty about the efficacy of the drug. As the trials included patients whose initial infection had not been cured, it is not clear how bezlotoxumab prevents the recurrence of something that has not resolved. Bezlotoxumab is not indicated for the treatment of *C. difficile* infection and it only had a significant effect on sustained cure in one of the trials (see Table). The optimum timing of the infusion

Table **Efficacy of bezlotoxumab in preventing recurrent infection with *Clostridium difficile***²

Trial	Number of patients	Recurrences	Sustained cure*	Recurrence rate in patients after initial clinical cure†
MODIFY I				
Bezlotoxumab	386	67 (17%)	232 (60%)	22% (67/299)
Placebo	395	109 (28%)	218 (55%)	33% (109/327)
MODIFY II				
Bezlotoxumab	395	62 (16%)	264 (67%)	19% (62/326)
Placebo	378	97 (26%)	197 (52%)	33% (97/294)

* Sustained cure was an initial clinical cure and no recurrent infection for 12 weeks.

† An initial clinical cure after antibiotic therapy was achieved by 80% of patients in the bezlotoxumab and placebo groups (pooled data).

and which patients are most likely to benefit will require further study. The drug is indicated for adults at 'high risk for recurrence' so its use will probably be limited to patients such as those over 65 years old, the immunocompromised and those with severe infections. However, bezlotoxumab has little effect on mortality. In the 12 weeks after the infusion 7.1% of the bezlotoxumab group and 7.6% of the placebo group died.² There will also be a need to compare bezlotoxumab to other management strategies, such as fidaxomicin, for preventing recurrences.

T manufacturer provided the product information

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

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

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NEW DRUGS

Aust Prescr 2018;41:200
<https://doi.org/10.18773/austprescr.2018.065>
 First published
 18 October 2018

Efmoroctocog alfa

Approved indication: haemophilia A

Eloctate (Bioverativ)

vials containing 250 IU, 500 IU, 750 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU

Australian Medicines Handbook: Appendix A

Haemophilia A is an inherited X-linked disorder that results in a deficiency of clotting factor VIII. A patient's risk of bleeding is influenced by the severity of the deficiency. To prevent or control bleeding the patient is given intravenous factor VIII. Nowadays a genetically engineered product is used in preference to products derived from plasma.

The half-life of some recombinant factor VIII products is 8–12 hours. This means that patients will need several injections a week to maintain an effective concentration of factor VIII. In contrast, the half-life of efmoroctocog alfa is 19 hours, so less frequent dosing may be possible.

Efmoroctocog is a genetically engineered molecule consisting of factor VIII linked to part of a human immunoglobulin (IgG Fc domain). The immunoglobulin component of this fusion protein binds to receptors in many cells and this delays the degradation of the factor VIII component.

The drug was first tested in 16 patients with severe haemophilia A. They were given a single dose of recombinant factor VIII and then a dose of efmoroctocog a few days later. Both drugs increased factor VIII activity, but efmoroctocog had a lower clearance. A more sustained response could be predicted.¹

To test the efficacy and safety of efmoroctocog, 165 patients, aged 12 years and above, were enrolled in an open-label trial. These patients all had severe haemophilia A and had bled at least 12 times in the previous year. They were managed either

with an individualised prophylactic regimen given every 3–5 days (118 patients), weekly prophylaxis (24 patients) or episodic treatment for bleeding (23 patients). The median duration of treatment was approximately 30 weeks. Approximately 45% of the patients taking individualised prophylaxis had no bleeding. Their annual bleeding rate was 2.9 compared with 8.9 for weekly prophylaxis and 37.3 for episodic treatment.²

During the phase III trial adverse events related to treatment occurred in 6.1% of the patients. These were most commonly arthralgia and malaise. No patients developed inhibitors to factor VIII.²

While efmoroctocog is eliminated more slowly than some other recombinant factor VIII products, it also takes longer for its effects to begin.¹ Whether the differences between the molecules lead to significant differences in clinical outcomes remains to be seen.

T T manufacturer provided additional useful information

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

At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration.

Erenumab

Approved indication: migraine

Aimovig (Novartis)

pre-filled pen containing 70 mg/mL

Australian Medicines Handbook section 16.3.2

Patients who have frequent attacks of migraine may benefit from prophylaxis. Drugs that have been used for prophylaxis include amitriptyline, pizotifen and propranolol. Injections of erenumab add to these choices.

Erenumab is a monoclonal antibody against the calcitonin gene-related peptide (CGRP) receptor. During an attack of migraine there is an increase in the concentration of CGRP. This peptide causes vasodilation and is thought to modulate pain. By competing with CGRP for the receptor, erenumab could prevent attacks.

After subcutaneous injection the peak concentration of erenumab is reached after 4–6 days. The effective half-life is 28 days so monthly injections are recommended. Renal and hepatic impairment are not expected to affect the pharmacokinetics. There is also no effect on the pharmacokinetics of the combined oral contraceptive pill. The safety of erenumab in pregnancy is unknown.

A double-blind, phase II clinical trial studied 667 adults with chronic migraine. They had an average of 18 days of migraine every month. There were 191 patients randomised to erenumab 70 mg, 190 to 140 mg and 286 to placebo. After receiving monthly injections for 12 weeks, 40–41% of the patients taking either dose of erenumab had a 50% or greater reduction in migraine days per month, compared with 23% of the placebo group. On average the reduction was 6.6 days with erenumab and 4.2 days with placebo.¹

The same doses were studied in a placebo-controlled phase III trial involving 955 patients with episodic migraine. In this trial the double-blind treatment was for 24 weeks. At the start of the trial the patients were having an average of 8.3 days of migraine per month. This was reduced by at least half in 43.3% (135/312) of the patients given erenumab 70 mg and 50% (159/318) of those given erenumab 140 mg. In the placebo group 26.6% (84/316) responded. The mean number of migraine days per month fell by 3.2 days with erenumab 70 mg, 3.7 days with 140 mg and by 1.8 days with placebo.²

In another phase III trial 286 patients with episodic migraine were randomised to receive erenumab 70 mg while 291 received monthly injections of placebo. After a 12-week double-blind treatment

phase, the mean number of migraine days fell by 2.9 days, from a baseline of 8.3 days, with erenumab, and by 1.8 days with placebo. A reduction of 50% or more in monthly migraine days was achieved by 39.7% of the erenumab group and 29.5% of the placebo group.³

During the clinical trials a total of 1400 patients were treated with erenumab. Injection site reactions were common, affecting 4–6% of patients. Pruritus, muscle spasm and constipation were also commonly reported. While some of the patients continued treatment with erenumab after the trials, its long-term safety is unknown. Some patients will develop anti-erenumab antibodies.^{2,3}

In its approved indication of migraine prophylaxis, erenumab is significantly more effective than placebo. Although the phase III trials reported that the difference is only 1–2 days per month, this can be important for patients having frequent migraine attacks. There were corresponding reductions in the number of days patients needed to take drugs for acute treatment. While there were some improvements in everyday functioning, these were not always significantly different from placebo.³

Erenumab will not benefit everyone. Less than half the patients injecting 70 mg monthly will get a 50% or greater reduction in the number of days they have migraine. Initially erenumab is likely to be tried in people who have not benefited from other drugs. Around 40% of the patients in the phase III trials had taken prophylaxis previously, but patients who had not responded to more than two preventive drugs were excluded from some trials.^{2,3} A monthly injection could overcome some of the problems with adhering to a prophylactic regimen, but the long-term effectiveness of erenumab needs to be established.

T manufacturer provided the product information

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<https://doi.org/10.18773/austprescr.2018.068>

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NEW DRUGS

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

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

Nabiximols

Approved indication: multiple sclerosis

Sativex (Emerge Health)

80 mg/mL pump metered dose spray

Australian Medicines Handbook section 16.5

Muscle spasticity occurs in more than two-thirds of patients with multiple sclerosis. Various drugs are used as muscle relaxants including baclofen and benzodiazepines. Nabiximols, a cannabinoid oromucosal spray, is indicated for moderate to severe spasticity that has not responded adequately to other treatments. The drug was approved in Australia in 2012, but only became available years later.

Nabiximols is derived from the *Cannabis sativa* plant. Each 100 microlitre spray contains delta-9-tetrahydrocannabinol (THC) 2.7 mg and cannabidiol 2.5 mg. It is thought that these cannabinoids act as agonists on the endocannabinoid system.

Trials have investigated the effect of self-titrated nabiximols spray as an add-on to other spasticity treatments in patients with multiple sclerosis (see Table).¹⁻³ The median daily dose in the studies was eight sprays. Response to treatment was scored by the patient each day using a numerical rating scale, ranging from zero (no spasticity symptoms) to 10 (worst possible symptoms).

Mean spasticity scores were decreased more with nabiximols than with placebo in a six-week¹ and a 15-week trial.² However, in the longer trial the difference between active treatment and placebo was not statistically significant (see Table).

In these trials, investigators observed that if a patient had not responded to nabiximols after four weeks, they were unlikely to respond at all.^{1,2} A trial with an enriched design was therefore planned. Only patients who had at least a 20% improvement in their spasticity symptoms after a four-week

single-blind period of nabiximols (241/572 patients) were randomised to receive nabiximols or placebo, double-blind, for a further 12 weeks.³ In the single-blind period the spasticity score decreased from 6.91 to 3.9 points. During the 12-week treatment phase, the mean scores continued to drop slightly with nabiximols but increased with placebo. Half of the patients who were not eligible to enrol in the 12-week phase had less than a 5% improvement in their spasticity symptoms after four weeks of nabiximols.

The long-term safety and efficacy of nabiximols was assessed in a trial of 36 patients who had been taking nabiximols for 3–4 years. Participants were randomised to either continue nabiximols or take a placebo. After four weeks, those in the nabiximols group were less likely to withdraw from the trial than those in the placebo group (44% vs 94%).⁴

The most common adverse effects with nabiximols include dizziness and fatigue, particularly at the beginning of treatment. Driving or operating machinery should be avoided if this occurs. Altered appetite, nausea, dry mouth, vertigo and diarrhoea have also been reported.

Depression, disorientation, dissociation and euphoric mood occur in up to 10% of people and treatment may need to be reduced or stopped if psychiatric symptoms occur. Delusions, hallucinations and paranoia were also reported. Nabiximols is contraindicated in patients with a personal or family history of psychotic illness or other significant psychiatric disorders.

Decreased muscle tone and strength can occur with nabiximols and falls were common in the trials. Nabiximols may have an additive effect on any drug with sedating effects, including alcohol.

After an oral spray, nabiximols is rapidly absorbed. It is highly lipophilic and distributes to body fat. Nabiximols has an initial half-life of 1–2 hours and

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Table Efficacy of self-titrated nabiximols for spasticity symptoms in multiple sclerosis

	Number of patients	Duration of treatment	Baseline spasticity scores*		Change in spasticity scores*		P value
			Nabiximols	Placebo	Nabiximols	Placebo	
Trial A ¹	184	6 weeks	5.49	5.39	–1.18	–0.63	0.048
Trial B ²	337	15 weeks	6.77	6.48	–1.05	–0.82	0.219
Trial C ³	572	4 weeks single blind	6.91	–	–3.01	–	–
	241 eligible to continue	12 weeks double blind	3.87	3.92	–0.04	0.81	0.0002

* Spasticity score was based on a 0–10 numerical rating scale recorded by the patient each day (0 – no spasticity, 10 – worst possible symptoms).

NEW DRUGS

a terminal half-life of 24–36 hours due to its slow release from fatty tissue. Plasma concentrations reached after a dose of nabiximols are much less than levels reached after smoking cannabis.

Nabiximols is not recommended during pregnancy. In animal studies, it was secreted in breast milk so it is contraindicated during breastfeeding.

Nabiximols is extensively metabolised in the liver by cytochrome P450 (CYP) enzymes. Concomitant treatment with a CYP3A4 inhibitor (e.g. ketoconazole, clarithromycin) or inducer (e.g. rifampicin, carbamazepine) may affect nabiximols exposure. If interacting drugs are started or stopped, the nabiximols dose may need to be re-titrated.

As there can be reactions at the site of application, the aerosol should be sprayed in the mouth at a different position each time (inside of cheek, under tongue). The dose should be titrated during the first two weeks, starting from one spray on day one, up to 12 sprays by day 14.

Nabiximols is the first cannabis-based medicine to be approved in Australia. It has been found to improve spasticity symptoms in less than half of patients. If improvements are not seen in the first four weeks, the patient is unlikely to benefit and treatment should be stopped.

T manufacturer provided the product information

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

At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration.

Correction

'Cephalosporin allergy' label is misleading [Correction]

Aust Prescr 2018;41:205

<https://doi.org/10.18773/austprescr.2018.061>

The article by Carlo L Yuson et al. on the 'cephalosporin allergy' label (*Aust Prescr* 2018;41:37-41) has been amended.

The general structure of cephalosporins, as depicted in Fig. 1, was corrected, as were several of the R1 side chain structures of cephalosporins and penicillins shown in the Table.

The original article has now been updated.

A:

ANSWERS TO SELF-TEST QUESTIONS

1 False 2 True

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