Australian Prescriber

AN INDEPENDENT REVIEW

nps.org.au/australian-prescriber

June 2019
Volume 42 Number 3

NPS MEDICINEWISE

CONTENTS

EDITORIAL

What's in complementary medicines?

Geraldine Moses
Adjunct associate professor, School of Pharmacy, University of Queensland, Brisbane

Consultant clinical pharmacist, Mater Health Services, Brisbane

Consultant pharmacist, Australian Dental Association

Keywords
complementary medicine, drug labelling, drug regulation, excipients

Aust Prescr 2019;42:82–3
https://doi.org/10.18773/austprescr.2019.024

Many millions of dollars are spent on complementary medicines by Australians every year, but these medicines are not without their risks. Adverse reactions are well documented such as the hepatotoxicity of black cohosh and comfrey.[1] There are also potential interactions between complementary medicines and prescription drugs, such as those that occur with St John's wort[2] and the catechins in green tea.[3]

Consumers and health professionals are increasingly aware that drug interactions with complementary medicines can alter the efficacy of conventional medicines and increase their toxicity. This is of particular concern during cancer chemotherapy.

Predicting drug interactions is complex and requires a comprehensive knowledge of the pharmacodynamics and pharmacokinetics of the ingredients of complementary medicines and the drugs they may interact with. Insight into the nature of drug-interaction literature and the strengths and weaknesses of drug-interaction checkers is also required. It is also helpful to understand the wide range of ingredients present in complementary medicines that contribute to drug interactions such as citrus bioflavonoids and black pepper. To do all this and assess drug interactions accurately, one needs to know all the ingredients in the products involved, not just the active ingredient.

Finding out the ingredients in a medicine should be as easy as reading the label or product information. This certainly is the case with registered medicines in Australia as they receive considerable scrutiny from the Therapeutic Goods Administration (TGA) after clinical trials. Their constituents must be declared, and the product information and associated labelling approved before the drug can be marketed.

In contrast, complementary medicines undergo little of this scrutiny. They are mostly classified by the TGA as 'listed' medicines, which by definition may only contain unscheduled ingredients with few public health concerns.[4] The regulatory pathway for listed medicines does not require proof of contents or efficacy or pre-approval of labelling and product information before marketing. A listing request is simply submitted online to the TGA and, once the necessary fee is paid, marketing is approved. As a result, the stated ingredients of complementary medicines are accepted on trust. There is no guarantee that the ingredients list is accurate.

Few Australian consumers or health professionals are familiar with how our drug regulatory system works. Most are unaware that complementary medicine labels may not be entirely trustworthy or that 'natural health products', especially those sourced from overseas, may contain undeclared adulterants such as banned substances or prescription drugs. In addition, most health professionals have little structured education regarding complementary medicines or of pharmacognosy (the science of the derivation of drugs from plants or other natural sources). They may not appreciate which details may be incorrect, misleading or neglected in the labelling and packaging of complementary medicines, or understand the potential therapeutic or toxicological effects of the constituents.

Despite these shortcomings, the labelling can still provide helpful and valid information for documenting complementary medicines within a patient's medication history. As with conventional medicines, it is insufficient to note only the active ingredients (e.g. 'Patient takes ginkgo, turmeric and selenium'). Instead, the brand name of the complementary medicine should be recorded, to show exactly which product the patient is taking along with its dose and duration. Without knowing the product name, a full assessment of which substances the patient is exposed to and their drug-interaction potential cannot be made.

In Australia listed and registered products are issued with an AUST L or AUST R number when included in the Australian Register of Therapeutic Goods (ARTG). This number must be printed on the front face of their packaging to indicate the product's legitimate inclusion in the ARTG. The number can be used to search the ARTG, via the TGA's website, to access the manufacturer's public declaration of ingredients. Absence of an AUST L or R number from the packaging may indicate a lack of permission for marketing the product in Australia.

The label should give the country of origin. Products from overseas are subject to manufacturing and regulatory processes that may be different from those of Australia so the level of assurance about the quality of the products will vary.

The more outlandish the therapeutic claims, the more likely the product may be unsafe or unreliable. The label can provide useful details about the formulation and any co-formulated ingredients such as alcohol

or caffeine. It may reveal which herbs are used in a herbal medicine.

For homeopathic products the label may give information about the potency. What is the base? If it is alcohol, what is the concentration? What are the active substances, and do they pose risks of cross allergy or toxicity? The 2015 NHMRC Statement on Homeopathy provides health professionals with a useful summary of this type of product.[5]

Although the ingredient lists on complementary medicines may be viewed with suspicion, it is often necessary to accept them at face value when making decisions with patients. In addition to assessing the potential risks and benefits of the main ingredient, attention should be paid to the co-formulated ingredients as these substances, often ignored, can represent a significant source of adverse effects and drug interactions.

A contemporary example is black pepper (*Piper nigram, P. longum*) containing piperine which is often included in turmeric products to enhance curcuminoid bioavailability. Piperine is a moderate inhibitor of cytochrome P450 (CYP) 3A4 and 2D6 and can therefore interact with a wide range of conventional medicines.[6] Other compounds like this are found in schisandra fruit and goldenseal root which also inhibit CYP3A4 and 2D6.[7] Catechins in green tea inhibit several organic anion-transporting polypeptides (drug transporters) and the antioxidant resveratrol inhibits CYP2C9 and CYP2D6.[8] Caffeine is another commonly ignored ingredient because people are often unaware that it is present in *Camellia sinensis*, guarana and yerbe mate. Yet the quantity of caffeine contained in a complementary medicine may cause significant stimulant effects.

Complementary medicines these days increasingly contain patentable preparations of so-called 'proprietary blends' of phytochemicals.[9] Even though the individual substances were originally derived from a natural source, these commercial combinations do not occur in nature and have never been administered to humans to determine safety, and so the pharmacological repercussions of their medicinal use are unknown.[9] We rely on consumers and health professionals to play an active role in monitoring the safety of these complementary medicines. Adverse events should be reported to the TGA.

In summary, although we cannot know for sure what is contained in most complementary medicines, we can know the products being taken. Product names and formulations should be documented in the patient's medication history rather than just the active ingredients so a comprehensive assessment can be made of the adverse effect and drug-interaction potential. <

Conflict of interest: none declared

REFERENCES

1. Stournaras E, Tziomalos K. Herbal medicine-related hepatotoxicity. World J Hepatol 2015;7:2189-93. https://doi.org/10.4254/wjh.v7.i19.2189
2. Borrelli F, Izzo AA. Herb-drug interactions with St John's wort (*Hypericum perforatum*): an update on clinical observations. AAPS J 2009;11:710-27. https://doi.org/10.1208/s12248-009-9146-8
3. Roth M, Timmermann BN, Hagenbuch B. Interactions of green tea catechins with organic anion-transporting polypeptides. Drug Metab Dispos 2011;39:920-6. https://doi.org/10.1124/dmd.110.036640
4. Therapeutic Goods Administration. Overview of listed complementary medicines [Internet]. 2017 Oct 29. www.tga.gov.au/overview-listed-complementary-medicines [cited 2019 May 1]
5. National Health and Medical Research Council. NHMRC statement: statement on homeopathy [Internet]. March 2015. www.nhmrc.gov.au/about-us/publications/evidence-effectiveness-homeopathy-treating-health-conditions [cited 2019 May 1]
6. Lee SH, Kim HY, Back SY, Han HK. Piperine-mediated drug interactions and formulation strategy for piperine: recent advances and future perspectives. Expert Opin Drug Metab Toxicol 2018;14:43-57. https://doi.org/10.1080/17425255.2018.1418854
7. Sprouse AA, van Breemen RB. Pharmacokinetic interactions between drugs and botanical dietary supplements. Drug Metab Dispos 2016;44:162-71. https://doi.org/10.1124/dmd.115.066902
8. Detampel P, Beck M, Krähenbühl S, Huwyler J. Drug interaction potential of resveratrol. Drug Metab Rev 2012;44:253-65. https://doi.org/10.3109/03602532.2012.700715
9. Gurley BJ, Yates CR, Markowitz JS. "...Not intended to diagnose, treat, cure or prevent any disease." 25 years of botanical dietary supplement research and the lessons learned. Clin Pharmacol Ther 2018;104:470-83. https://doi.org/10.1002/cpt.1131

FURTHER READING

Memorial Sloan Ketting Cancer Center. About herbs database [Internet]. www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs/search [cited 2019 May 1]

LETTERS

Letters to the Editor

Irritable bowel syndrome diagnosis

Aust Prescr 2019;42:84
https://doi.org/10.18773/austprescr.2019.027

I found some of the statements in the article about irritable bowel syndrome confusing.[1]

First, there is the statement that 'irritable bowel syndrome is not a diagnosis of exclusion'. The article then says that the diagnosis is made on symptoms fulfilling the Rome IV diagnostic criteria and the absence of red flags, which include the absence of iron deficiency anaemia and a negative faecal occult blood test. It also recommends testing for urea and electrolytes, C-reactive protein, liver function tests, faecal calprotectin and that testing for coeliac disease should be considered.

The article also states 'the symptoms of irritable bowel syndrome share similarities with inflammatory bowel disease and gastrointestinal malignancies'. This statement suggests that the presence of symptoms alone cannot make a positive diagnosis of irritable bowel syndrome. There are no features that are unique only to irritable bowel syndrome.

Second, there is also the confusing statement 'There is no role for a faecal occult blood test to exclude gastrointestinal malignancy in patients with symptoms of irritable bowel syndrome'. However, the absence of red flags mandates a negative faecal occult blood test (see Box 2 of the article).

How can irritable bowel syndrome be a positive diagnosis when the diagnostic process involves the exclusion of alternative, more sinister diagnoses?

Nick Tyllis
General practitioner
Alice Springs, NT

REFERENCE

1. Basnayake C. Treatment of irritable bowel syndrome. Aust Prescr 2018;41:145-9. https://doi.org/10.18773/austprescr.2018.044

Chamara Basnayake, the author of the article, comments:

The letter highlights the common diagnostic dilemmas in irritable bowel syndrome. As the paper focused on treatment, the nuances and controversies surrounding diagnosis were not detailed.

The diagnosis is made on the basis of symptoms obtained from the patient's history, as described by the Rome criteria, in the absence of red flags. When the symptoms are unclear, or there is an obvious red flag in the history, further testing is recommended.

Diagnostic testing is not required to rule red flags in or out. Box 2 of the article was titled 'Red flags that require further testing or specialist assessment'. It does not include conditions that require ruling out in order to diagnose irritable bowel syndrome. Red flags prompt the doctor to investigate the potential for alternative, more sinister diagnoses.

Faecal occult blood testing has been proven exclusively for screening populations to improve the early detection of colorectal cancer. It is not helpful as a diagnostic tool in people with symptoms. A false-negative faecal occult blood result in symptomatic individuals may inappropriately reassure doctors not to proceed with further investigations.[1]

It is true that there are many similarities in the symptoms of organic and functional gastrointestinal disorders. There is no unique symptom that positively diagnoses irritable bowel syndrome. Similarly, chest pain is not solely a symptom of ischaemic heart disease. An appropriate history should include an assessment of risk factors for organic gastrointestinal conditions, including a family history of gastrointestinal malignancies, or coeliac disease. The use of non-invasive testing is at the discretion of the doctor assessing a patient. If a red flag is identified on non-invasive testing, endoscopies should be arranged.

REFERENCE

1. Friedman A, Chan A, Chin LC, Deen A, Hammerschlag G, Lee M, et al. Use and abuse of faecal occult blood tests in an acute hospital inpatient setting. Intern Med J 2010;40:107-11. https://doi.org/10.1111/j.1445-5994.2009.02149.x

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

Denosumab and osteonecrosis of the jaw

Aust Prescr 2019;42:85
https://doi.org/10.18773/austprescr.2019.028

I wish to remind readers of the association between bisphosphonates and osteonecrosis of the jaw.[1] I am concerned that the clinical trial data supporting the approval of injectable denosumab in Australia,[2] for treating osteoporosis in postmenopausal women, may have underestimated the risk of osteonecrosis.

The main placebo-controlled trial involved more than 7000 osteoporotic postmenopausal women aged between 60 and 90 years. The diagnosis of osteoporosis was defined as a bone mineral density T-score of less than minus 2.5 at the lumbar spine, hip or both. Women were excluded from the trial if they had taken an oral bisphosphonate for more than three years.[3]

After 36 months, osteonecrosis of the jaw had not been reported in the active treatment group of almost 4000 women. However, this result cannot be extrapolated to the large cohort of Australian women who have taken oral bisphosphonates for more than three years. These drugs have been widely prescribed for more than 20 years so there is a large cohort of women potentially at risk.

The incidence of osteonecrosis of the jaw in women given denosumab after prolonged exposure to oral bisphosphonates is unknown. Until this is determined, the risk of developing osteonecrosis of the jaw should be assumed to be higher than in women not previously exposed to bisphosphonates.

There is a suspicion that dentists and oral surgeons under-report osteonecrosis of the jaw as an adverse drug reaction. This may possibly be for fear of claims of negligence if osteonecrosis follows a dental procedure.

I believe prescribers have a responsibility to warn of osteonecrosis of the jaw when obtaining consent to prescribe denosumab to patients who have been exposed to oral bisphosphonates for more than three years. These patients should be referred for a dental assessment before starting denosumab. They should also inform their dentist if they are taking or have previously taken bisphosphonates.

Osteonecrosis of the jaw can be a debilitating and disfiguring condition. Life is difficult without a mandible.

Robert Bower
Clinical associate professor, Faculty of Health and Medical Sciences, UWA Dental School, University of Western Australia, Perth
Periodontist, West Perth, WA

REFERENCES

1. Goss A, Backhouse P. Medicinal mishap: Bisphosphonates and osteonecrosis of the jaws. Aust Prescr 2007;30:96-7. https://doi.org/10.18773/austprescr.2007.058
2. Department of Health, Therapeutic Goods Administration. Australian Public Assessment Report: Denosumab. Submission number PM-2009-00390-3-5. 2011 Jan 27. pp. 29-30. www.tga.gov.au/auspar/auspar-denosumab-2 [cited 2019 May 1]
3. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al; FREEDOM trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361;756-65. https://doi.org/10.1056/NEJMoa0809493

ARTICLE

When should I take my medicines?

Louise Grannell
Senior medicines information pharmacist, Alfred Health, Melbourne

Keywords
patient adherence, antihypertensives, chronotherapy, drug administration

Aust Prescr 2019;42:86–9
https://doi.org/10.18773/austprescr.2019.025

SUMMARY

Adherence to drug regimens is critical to optimise therapeutic outcomes. To aid adherence patient preferences must be discussed when considering the timing of doses, especially for chronic therapy.

The appropriate timing of administration should maximise therapeutic effects and minimise adverse reactions. If possible, doses should fit with the patient's daily routines.

Check if drug absorption is affected by meals. Food may increase or decrease absorption, and may also improve gastric tolerance.

Non-steroidal anti-inflammatory drugs are usually taken with food. For patients with acute pain, administration without food may be acceptable.

The best time to take antihypertensive drugs is uncertain. Chronotherapy studies may clarify any influence of evening or morning doses on clinical outcomes.

Introduction

Should the medicine be taken with or without food? What time is best to take my medicine – in the morning or at night? These are common questions posed by patients, especially when starting a new drug. For some drugs, incorrect timing may result in reduced efficacy (e.g. the progestogen-only pill) or poor tolerability. For others the significance of timing is unclear, for example do all statins need to be taken at night?

Appropriate administration should balance timing with patient preferences, especially for drugs used to treat chronic diseases for which adherence rates can be as low as 50%.[1] Strategies to optimise adherence include establishing the patient's preferences about the timing of doses, ensuring patients understand the importance of taking doses in relation to food, and simplifying the frequency of administration to once daily, for example using slow-release formulations, when possible.[2,3]

With or without food?

Specific recommendations for dosing oral medicines in relation to food are available for approximately 40% of commonly prescribed drugs.[4] Recommendations, along with practical advice, are included in most prescribing and dispensing systems, and in resources such as the Australian Medicines Handbook. There can be discrepancies in the advice given by different sources. This can be due to the approved product information not being updated when new clinical information becomes available.

Several factors influence drug administration in relation to food, including pharmacokinetics, efficacy and, in particular, improving patient tolerance by minimising gastrointestinal upset (Table).

Pharmacokinetic food-effect studies assessing drug absorption are undertaken during drug development and inform the product information. Although food may alter the extent or rate of absorption through various mechanisms,[5,6] not all pharmacokinetic effects are clinically relevant and some, such as flucloxacillin, are being reviewed.

Meal times can serve as a prompt for patients to remember to take their medicines, so instructions to take on an empty stomach may decrease adherence. If the desired therapeutic response is obtained, the question of taking a drug with food is less important. For example, levothyroxine is best absorbed on an empty stomach, however if adherence is of concern, it can be given consistently in relation to food[7] and doses adjusted according to thyroid function tests. As a general rule, drugs for chronic diseases should be taken at consistent times relative to meals.

What time of day is best?

Information on the appropriate time of day to take medicines is often lacking. Only a limited number of drugs specify a time of day,[4] but including explicit directions around timing on the labels applied at the pharmacy during dispensing is encouraged to help patients safely take their drugs.[8] The timing of doses is important in some cases to avoid adverse effects, such as taking bisphosphonates in the morning once the patient is up and about to minimise the risk of oesophageal ulceration, and taking drugs with sedative effects at bedtime to minimise daytime

Table **Taking medicines with or without food**

Factors to consider	Clinically relevant examples
Absorption: Will absorption be impaired or enhanced if taken with food?	• If absorption is significantly impaired by food, give the drug at least 30 minutes before food, e.g. bisphosphonates such as alendronate, metronidazole benzoate (liquid)*, rifampicin. • If absorption is significantly increased with food, give the drug with or after a meal, e.g. griseofulvin, some antiretrovirals. • If absorption is impaired by food but tolerance is a concern, the drug can be given with food, e.g. erythromycin base*, roxithromycin, sodium fusidate.
Therapeutic effects: Will the drug be more effective if taken with or without food?	• Phosphate binders, e.g. calcium carbonate, must be taken with food to bind dietary phosphate in the gastrointestinal tract to decrease phosphate absorption. • Sulphonylureas are given with food to decrease the risk of hypoglycaemia.
Gastrointestinal factors: Will the drug be better tolerated if taken with or soon after food?	• To minimise gastrointestinal upset, including nausea and vomiting, give the drug with or soon after food, e.g. azathioprine, corticosteroids, erythromycin ethyl succinate, metformin, metronidazole*.

Compiled from the product information and the Australian Medicines Handbook.
* variable depending on salt

sedation. In general, appropriate timing must always be balanced with optimising adherence to treatment.

Diseases such as asthma and rheumatoid arthritis have circadian patterns in intensity and symptoms. Blood pressure displays a circadian variation by decreasing overnight.[9] There is therefore renewed interest around the impact of circadian variation on dose timing.[9-11]

Chronotherapy is the practice of altering the timing of doses in relation to individual circadian rhythms to improve efficacy and to minimise adverse effects.[11] This is important for corticosteroids, as cortisol release by the adrenal cortex follows a circadian rhythm.[11] Evidence for chronotherapy-based timing for other drugs is very limited, but is growing for antihypertensives and there is currently a large long-term study underway of nocturnal versus morning doses of antihypertensive drugs.[12]

Antibiotics

The appropriate dose and frequency of an antibiotic is determined clinically based on indication, severity of infection, and renal or hepatic function. Administration of antibiotics given more than once daily should be spaced as evenly as possible during waking hours. Examples of once-daily dosing include trimethoprim, taken at bedtime to maximise urinary concentrations overnight, and doxycycline, taken in the morning with food and a large glass of water or milk to reduce the risk of oesophageal ulcers.

Many antibiotics have recommendations regarding timing with meals. Of interest is ciprofloxacin which is approved to be taken irrespective of food, yet formation of non-absorbable complexes with metallic ions, such as in calcium-rich food, has resulted in recommendations to take ciprofloxacin on an empty stomach.[4,6]

A recent study[13] reviewed pharmacokinetic data for flucloxacillin and found that food decreased total flucloxacillin concentrations. However, concentrations of free flucloxacillin that are associated with efficacy were obtained in most circumstances. These results suggest that there could be flexibility with flucloxacillin administration, which may have significant implications for simplifying administration.

Antidepressants

Antidepressants with sedative potential are recommended to be taken at bedtime. Examples are mianserin, mirtazapine and tricyclic antidepressants, including low-dose amitriptyline commonly used for neuropathic pain. Antidepressants such as selective serotonin reuptake inhibitors which can cause insomnia are recommended to be taken in the morning. However, fluvoxamine and, to a lesser extent, paroxetine can cause somnolence and may need to be given in the evening.[14] Some antidepressants such as duloxetine and venlafaxine are considered to have a minimal risk of sedation, so timing is guided by patient preference and tolerance.

Corticosteroids

Cortisol release by the adrenal cortex follows a circadian rhythm. Concentrations are higher in the morning and lower in the evening. Maintenance doses should therefore be given in the morning (with food) to mimic normal cortisol production and minimise adrenocortical suppression.[9]

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended to be taken with food to reduce the incidence of gastrointestinal adverse effects. There are no published studies proving that food modifies the gastric damage caused by NSAIDs,[15] although patients anecdotally report improved tolerance with food. In acute pain, NSAIDs (especially ibuprofen) may be taken on an empty stomach to achieve higher plasma drug concentrations and an earlier analgesic effect. This may prevent patients taking unnecessary 'extra' doses of analgesia.[16] The short-term use of over-the-counter NSAIDs appears to be safe with a low occurrence of severe ulcer complications, despite the uncertainty around the influence of food.[16] Patients at high risk of NSAID-induced peptic ulcers may benefit more from prophylaxis, such as proton pump inhibitor therapy, rather than taking NSAIDs with food.[17]

Proton pump inhibitors

The appropriate timing of proton pump inhibitor therapy depends on the indication and patient preference. In gastro-oesophageal reflux disease, the drug should be taken half an hour before breakfast if symptoms primarily occur during the day, or half an hour before the evening meal if they occur at night.[18] Taking the proton pump inhibitor before food may be beneficial when starting therapy or for intermittent use in symptomatic patients to ensure a high plasma concentration is available to bind to the active proton pumps.[19] The timing with food or at specified times of day does not appear critical for other indications, as proton pump inhibitors achieve maximal acid suppression in two to three days.[19]

Statins

Statins lower cholesterol concentrations by inhibiting the enzyme 3-hydroxy 3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This follows a circadian rhythm and is principally produced between midnight and 6 am. Statins with a shorter half-life such as simvastatin and pravastatin are therefore recommended for evening dosing. Longer acting statins such as atorvastatin and rosuvastatin may be taken at any time.

A 2016 Cochrane review of chronotherapy-based dosing concluded that evening dosing of short-acting statins does not confer an additional benefit over morning dosing in terms of clinically relevant changes in lipids.[20] Patients should therefore take statins at a time that will optimise adherence. Further studies are needed to analyse whether chronotherapy affects clinical cardiovascular outcomes.

Antihypertensives

Blood pressure has a circadian variation. Patients whose blood pressure lowers during the night tend to experience fewer cardiovascular events compared to those whose blood pressure barely dips. This can be detected by 24-hour blood pressure monitoring. A hypothesis follows that nocturnal dosing of antihypertensives may be more cardioprotective than morning dosing.[21]

An early single-centre study of 2156 patients reported a reduction in cardiovascular events with nocturnal dosing of one or more antihypertensive drugs versus taking all antihypertensives in the morning.[22] However this result was subject to criticism. A larger study in around 18,000 hypertensive patients also concluded that bedtime ingestion of one or more antihypertensives was associated with a significantly lower risk of cardiovascular morbidity and mortality.[23] The Treatment in Morning versus Evening (TIME) trial randomised 21,000 patients to take all their antihypertensive drugs either in the morning or evening. Its results are expected in late 2019.[12]

Whether the combined outcomes from these large chronotherapy studies will influence the timing of doses in international guidelines remains to be seen. In the interim, antihypertensive drugs may be taken consistently at a time of day that maximises adherence.

Diuretics are given in the morning, as diuresis at night may interfere with sleep and increases the risk of falls in older patients. If patients require twice-daily dosing, the diuretic potency determines the appropriate timing of the second dose. For potent loop diuretics, give the second dose at midday. For hydrochlorothiazide or amiloride, give the second dose before 6 pm.

Other resources

In addition to reviewing prescribing information and resources such as the Australian Medicines Handbook, consultation with a pharmacist or a medicines information centre may be helpful. They have access to specialised drug-interaction resources which can determine the clinical relevance of food on drug absorption and can source new research into the optimal timing of drug administration.

Conclusion

Encouraging patients to take their medicines to best fit in with their daily routine will optimise adherence. To further improve therapeutic outcomes, patients must understand the appropriate timing of doses

relative to food intake and time of day. To help patient-centred discussions, health professionals should regularly update their knowledge about the appropriate timing of administration. ≺

Conflict of interest: none declared

Acknowledgement: Thank you to Linda Graudins, Advanced practice pharmacist and Medication safety lead, Alfred Health, and Ingrid Hopper, Clinical pharmacologist, Alfred Health, for their manuscript editing and robust discussions.

REFERENCES

1. Sabaté E, editor. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003. https://www.who.int/chp/knowledge/publications/adherence_report/en [cited 2019 May 1]
2. Usherwood T. Encouraging adherence to long-term medication. Aust Prescr 2017;40:147-50. https://doi.org/10.18773/austprescr.2017.050
3. National Institute for Health and Care Excellence. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. Clinical guideline (CG76). London: NICE; 2009. www.nice.org.uk/guidance/cg76/chapter/introduction [cited 2019 May 1]
4. Samson L, editor. Australian pharmaceutical formulary and handbook: the everyday guide to pharmacy practice. 24th ed. Canberra: Pharmaceutical Society of Australia; 2018. https://www.psa.org.au/media-publications/australian-pharmaceutical-formulary [cited 2019 May 1]
5. Deng J, Zhu X, Chen Z, Fan CH, Kwan HS, Wong CH, et al. A review of food-drug interactions on oral drug absorption. Drugs 2017;77:1833-55. https://doi.org/10.1007/s40265-017-0832-z
6. McLachlan A, Ramzan I. Meals and medicines. Aust Prescr 2006;29:40-2. https://doi.org/10.18773/austprescr.2006.026
7. Roberts GW. Taking care of thyroxine. Aust Prescr 2004;27:75-6. https://doi.org/10.18773/austprescr.2004.061
8. La Caze A. Safer dispensing labels for prescription medicines. Aust Prescr 2018;41:46-9. https://doi.org/10.18773/austprescr.2018.009
9. Kaur G, Phillips CL, Wong K, McLachlan AJ, Saini B. Timing of administration: for commonly-prescribed medicines in Australia. Pharmaceutics 2016;8:13. https://doi.org/10.3390/pharmaceutics8020013
10. Kaur G, Phillips C, Wong K, Saini B. Timing is important in medication administration: a timely review of chronotherapy research. Int J Clin Pharm 2013;35:344-58. https://doi.org/10.1007/s11096-013-9749-0
11. Selfridge JM, Gotoh T, Schiffhauer S, Liu J, Stauffer PE, Li A, et al. Chronotherapy: intuitive, sound, founded... but not broadly applied. Drugs 2016;76:1507-21. https://doi.org/10.1007/s40265-016-0646-4
12. Rorie DA, Rogers A, Mackenzie IS, Ford I, Webb DJ, Willams B, et al. Methods of a large prospective, randomised, open-label, blinded end-point study comparing morning versus evening dosing in hypertensive patients: the Treatment In Morning versus Evening (TIME) study [abstract]. BMJ Open 2016;6:e010313. https://doi.org/10.1136/bmjopen-2015-010313
13. Gardiner SJ, Drennan PG, Begg R, Zhang M, Green JK, Isenman HL, et al. In healthy volunteers, taking flucloxacillin with food does not compromise effective plasma concentrations in most circumstances. PLoS One 2018;13:e0199370. https://doi.org/10.1371/journal.pone.0199370
14. Taylor D, Barnes TR, Young AH. The Maudsley prescribing guidelines in psychiatry. 13th ed. Hoboken (NJ): Wiley; 2019.
15. Moore RA, Derry S, Wiffen PJ, Straube S. Effects of food on pharmacokinetics of immediate release oral formulations of aspirin, dipyrone, paracetamol and NSAIDs - a systematic review. Br J Clin Pharmacol 2015;80:381-8. https://doi.org/10.1111/bcp.12628
16. Rainsford KD, Bjarnason I. NSAIDs: take with food or after fasting? J Pharm Pharmacol 2012;64:465-9. https://doi.org/10.1111/j.2042-7158.2011.01406.x
17. Drini M. Peptic ulcer disease and non-steroidal anti-inflammatory drugs. Aust Prescr 2017;40:91-3. https://doi.org/10.18773/austprescr.2017.037
18. Keung C, Hebbard G. The management of gastro-oesophageal reflux disease. Aust Prescr 2016;39:6-10. https://doi.org/10.18773/austprescr.2016.003
19. Wilder-Smith C, Röhss K, Bokelund Singh S, Sagar M, Nagy P. The effects of dose and timing of esomeprazole administration on 24-h, daytime and night-time acid inhibition in healthy volunteers. Aliment Pharmacol Ther 2010;32:1249-56. https://doi.org/10.1111/j.1365-2036.2010.04469.x
20. Izquierdo-Palomares JM, Fernandez-Tabera JM, Plana MN, Añino Alba A, Gómez Álvarez P, Fernandez-Esteban I, et al. Chronotherapy versus conventional statins therapy for the treatment of hyperlipidaemia. Cochrane Database Syst Rev 2016;CD009462. https://doi.org/10.1002/14651858.CD009462.pub2
21. MacDonald T. Is dosing time important for treating hypertension? Prescr 2015;26:33-4. https://www.prescriber.co.uk/article/is-dosing-timeg-hypertension [cited 2019 May 1]
22. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. Chronobiol Int 2010;27:1629-51. https://doi.org/10.3109/07420528.2010.510230
23. Hermida RC, Crespo JJ, Otero A, Domínguez-Sardiña M, Moyá A, Ríos MT, et al.; Hygia Project Investigators. Asleep blood pressure: significant prognostic marker of vascular risk and therapeutic target for prevention. Eur Heart J 2018;39:4159-71. https://doi.org/10.1093/eurheartj/ehy475

ARTICLE

Adolescent self-harm: think before prescribing

Joel King
Consultant child and adolescent psychiatrist and Psychiatry training coordinator, Professorial Unit, The Melbourne Clinic

Senior lecturer, Department of Psychiatry, University of Melbourne

Sonja Cabarkapa
Psychiatry registrar, St Vincent's Hospital, Melbourne

Fiona Leow
Consultant psychiatrist, Eating Disorders Unit, Royal Melbourne Hospital

Keywords
drug overdose, self-inflicted injury, suicide

Aust Prescr 2019;42:90–2
https://doi.org/10.18773/austprescr.2019.023

SUMMARY

The assessment of self-harm in adolescence should include identifying medical complications and any underlying psychiatric conditions.

Changes in the frequency, type, and severity of self-harm can signify increasing suicidality and progression towards lethal action. As 30% of adolescent self-harm involves an overdose of prescription drugs, prescribing limited quantities and having the parents hold the supply can decrease this risk.

Individual psychological therapies are first line. They can be combined with school and parental involvement.

There is very little evidence supporting the use of psychotropic drugs for treating adolescent self-harm.

Introduction

Adolescent self-harm is a common but complex issue faced by GPs. The second Australian Child and Adolescent Survey of Mental Health and Wellbeing found 10% of teenagers reported that they had previously harmed themselves. Self-harm was twice as high in females than in males.[1] The survey defined self-harm as deliberately hurting or injuring oneself without intent to suicide, often done secretly. This encompasses both self-injury and self-poisoning. Self-injury refers to deliberate, self-inflicted destruction of body tissue resulting in immediate damage, without suicidal intent, including cutting, scratching and self-battery.[2] Self-poisoning refers to intentionally taking a poisonous substance believing that it will be noxious.[3]

Causes of self-harm

There are several aetiological theories for self-harm. The distraction hypothesis suggests self-harm diverts attention from emotional pain to physical sensations. Another theory describes self-harm leading to endogenous opioid release and an analgesic effect. The self-verification concept proposes self-harm communicates adolescents' negative views about themselves to others. Accordingly, self-harm is best seen as a heterogeneous phenomenon with complex internal and external factors.[4]

Contextual factors include sexual abuse, bullying, sexuality difficulties, poor academic performance, school refusal, family dysfunction, abusive online contacts, and self-harming peers. The nature of stressors varies with age. Younger adolescents commonly describe familial stress. Older adolescents are more likely to describe peer-related stress.[5]

Assessment

The initial assessment should exclude medical complications, such as neurovascular damage and infection. If the history shows changes in self-harm frequency, type and severity, this can signify increasing suicidality and progression towards taking lethal action.

It is important to screen for psychiatric disorders that often first present in adolescence, such as depression, anxiety disorders, eating disorders, emerging psychosis, and substance use disorders. Enquiring about the adolescent's ways of coping with different stresses may reveal emerging personality traits and disorders. However, caution is needed around making definitive diagnoses due to ongoing identity formation and frontal cortical development in adolescence. These processes contribute to maturation of reasoning, goal setting and impulse control.[6] Active psychiatric disorders such as depression impair cognition and problem-solving and can mistakenly give the impression of a personality disorder. A thorough developmental history and psychiatric referral may assist this differentiation. Adolescents with a suspected emerging psychosis should be assessed urgently, especially if there is a family history of mood or psychotic disorders.

Management

Adolescents are more likely to reduce their self-harm behaviours when underlying stressors are addressed or when they learn other ways of coping. Given that self-harm is often a coping strategy taken up in desperation, simply telling the adolescent to stop is unhelpful and invalidating.

Many mental disorders presenting in adolescence can be treated with psychological therapy and unnecessary prescribing can be avoided. Some schools have excellent wellbeing coordinators and counsellors who may be able to provide a safe school-based space and basic psychological assistance. An external therapist should be sought for more structured therapies such as cognitive or dialectical behavioural therapy. Both the Royal Australian and New Zealand College of Psychiatrists and the Australian Psychological Society websites have directories of practitioners.[7,8] Headspace services have psychologists and sometimes a visiting child and adolescent psychiatrist.[9] Public child and youth mental health services usually become involved in more severe, complex cases with significant family dysfunction, ongoing self-harm, case-management needs, and coordination between multiple agencies, such as child protection.

Poor sleep is correlated with self-harm. Sleep hygiene education should be provided.[10]

Parental involvement

Parents may be needed for practical issues, such as booking and paying for appointments, and addressing stressors that the adolescent cannot solve on their own. These include family conflict, unreasonable school or parental expectations, and bullying. Some parents require separate therapy where they learn to contain their own anxiety and provide support and validation for their teenager. This can run alongside individual therapy for the adolescent, with all clinicians in regular contact to ensure a consistent understanding of the clinical situation and management plan.

Confidentiality

The adolescent may not want their parents to know about their self-harm, usually fearing their parents will not understand, blame them, or simply tell them to stop their behaviour. While respecting these concerns, involving parents can help the adolescent feel less alone and better supported. Such fears should be addressed by speaking first with the adolescent about a shared, non-judgemental understanding of the behaviour, and offering to speak with the parents while the adolescent is in the room. Negotiating what the adolescent is willing to share with their parents is crucial. This may take several sessions before sufficient trust is built for the adolescent to involve their parents.

Occasionally, there is extremely dangerous self-harm which requires acute intervention. This can include urgent involuntary treatment under the relevant mental health act, usually when the patient cannot give informed consent, refuses treatment, and poses an acute risk to themselves or others. In these situations, the GP should also consider informing the parents, which may be against the adolescent's wishes, and explain the reasons for doing so. This requires a careful balance between respecting doctor–patient confidentiality and supporting crucial caregivers.[11]

Preventing harm

Identifying early warning signs and formulating an agreed plan with all parties can reduce further episodes of self-harm. A useful tool is the traffic light system where the adolescent identifies what feelings and behaviours occur at different colours (see Table) and what the responses should be at each stage.[12] The patient, family and clinicians follow the plan and update it if required.

The traffic light approach can ensure a consistent management response when the overwhelmed adolescent is unlikely to produce a coherent description of their emotional state and needs. This is due to cortical dysfunction of higher brain regions, with reliance on lower, brainstem-level responses. At this time, a lengthy discussion about stressors and feelings is likely to cause more distress. It is better to talk when patients return to 'green' and can reflect

Table **An example of a traffic light management plan for the prevention of adolescent self-harm**

Early warning signs	• **Not sleeping well** • **Not attending my extracurricular activities, e.g. soccer** • **Becoming irritable at small things**	
Traffic light	**My thoughts and behaviour**	**My plan**
Green	• Stress level minimal • Going to school • Engaging with family and friends • Few thoughts of self-harm	• Continue with sleep hygiene • Write in journal when feeling stressed • Play soccer with friends
Orange	• Stress level moderate • Increased time checking social media • Comfort eating • Withdrawing to my room	• Listen to my favourite music • Use rubber band technique • Go for a short walk with Dad and the dog
Red	• Feeling overwhelmed • 'I can't problem-solve or talk anymore' • 'I hate myself and the world' • 'I want to cut myself now'	• Hold ice cubes tightly • Parents, please sit with me but don't talk to me • Parents, ensure no access to blades • Parents, reduce overall stimulation for me • Parents, help me call Lifeline

more clearly. Phrases with 'What led to ...' and 'And then what happened?' may be more acceptable than questions starting with 'Why?'

Education and harm minimisation are important tools, especially for adolescents with repetitive patterns of self-harm. Most adolescents are unaware of the potential for self-harm to cause serious damage, morbidity or even death.[13] Preventing harm may involve offering a less dangerous alternative that achieves a similar sensation. Examples include flicking a rubber band around the wrist, temporarily holding ice cubes, or doing exercise such as push-ups. Tailored distraction techniques such as listening to music or playing a game can be helpful. Restricting access to implements, such as razor blades, knives, pills and firearms, is recommended but insufficient alone. These restrictions are often circumvented by desperate adolescents.

Drug therapy

There are no pharmacological trials focusing on reducing repetitive deliberate self-harm in children or adolescents. In adults, the small number of randomised controlled trials found that drug treatment does not reduce the risk of repeated self-harm.[14]

Psychotropic drugs may have a role in treating severe underlying psychiatric disorders that do not respond to psychological interventions, but these cases should be referred to a child and adolescent psychiatrist. The limited evidence base should be explained to the patient and family. If a prescription is issued, prescribe limited quantities and ask the parents to hold and dispense the drugs as this can reduce the risk of overdose.[15]

About 30% of self-harm is by overdose with prescription drugs, most commonly benzodiazepines, antidepressants and amphetamines.[16,17] Medicines are often combined with alcohol and recreational drugs in impulsive overdoses.[18] This is unsurprising as many of these substances reduce inhibition. Motivational interviewing and limiting access are reasonable first steps to reduce the abuse of these substances.

Conclusion

Adolescent self-harm represents a common group of behaviours that are best addressed through psychological means. This may involve the family and the school. Prescription drugs have nearly no evidence supporting their use in this age group and should be avoided. ◀

Joel King has received honoraria for providing independent medical education at a symposium funded by Servier.

REFERENCES

1. Lawrence D, Johnson S, Hafekost J, Boterhoven de Haan K, Sawyer M, Ainley J, et al. The mental health of children and adolescents: report on the second Australian Child and Adolescent Survey of Mental Health and Wellbeing. Canberra: Commonwealth of Australia; 2015. http://www.health.gov.au/internet/main/publishing.nsf/Content/mental-pubs-m-child2 [cited 2019 May 1]
2. Swannell SV, Martin GE, Page A, Hasking P, St John NJ. Prevalence of nonsuicidal self-injury in nonclinical samples: systematic review, meta-analysis and meta-regression. Suicide Life Threat Behav 2014;44:273-303. https://doi.org/10.1111/sltb.12070
3. Bancroft JH, Skrimshire AM, Reynolds F, Simkin S, Smith J. Self-poisoning and self-injury in the Oxford area. Epidemiological aspects 1969-73. Br J Prev Soc Med 1975;29:170-7. https://doi.org/10.1136/jech.29.3.170
4. Kirtley OJ, O'Carroll RE, O'Connor RC. Pain and self-harm: a systematic review. J Affect Disord 2016;203:347-63. https://doi.org/10.1016/j.jad.2016.05.068
5. Hazel NA, Oppenheimer CW, Technow JR, Young JF, Hankin BL. Parent relationship quality buffers against the effect of peer stressors on depressive symptoms from middle childhood to adolescence. Dev Psychol 2014;50:2115-23. https://doi.org/10.1037/a0037192
6. Crews F, He J, Hodge C. Adolescent cortical development: a critical period of vulnerability for addiction. Pharmacol Biochem Behav 2007;86:189-99. https://doi.org/10.1016/j.pbb.2006.12.001
7. Your Health in Mind. Find a psychiatrist [Internet]. Melbourne: The Royal Australian & New Zealand College of Psychiatrists; 2019. https://www.yourhealthinmind.org/find-a-psychiatrist [cited 2019 May 1]
8. Australian Psychological Society. Find a psychologist [Internet]. Melbourne: APS; 2018. https://www.psychology.org.au/Find-a-Psychologist [cited 2019 May 1]
9. Headspace [Internet]. Headspace National Youth Mental Health Foundation Ltd; 2019. http://www.headspace.org.au [cited 2019 May 1]
10. Hysing M, Sivertsen B, Stormark KM, O'Connor RC. Sleep problems and self-harm in adolescence. Br J Psychiatry 2015;207:306-12. https://doi.org/10.1192/bjp.bp.114.146514
11. Mental Health Act. 2014. No. 26 of 2014. Authorised version no. 018 incorporating amendments as at 1 April 2018. http://www.legislation.vic.gov.au/Domino/Web_Notes/LDMS/PubStatbook.nsf/f932b66241ecf1b7ca256e92000e23be/0001F48EE2422A10CA257CB4001D32FB/$FILE/14-026abookmarked.pdf [PDF] [cited 2019 May 1]
12. Croucher S, Williamson GR. Risk assessment in mental health: introducing a traffic light system in a community mental health team. Open Nurs J 2013;7:82-8. https://doi.org/10.2174/1874434620130529004
13. Fortune SA, Hawton K. Deliberate self-harm in children and adolescents: a research update. Curr Opin Psychiatry 2005;18:401-6. https://doi.org/10.1097/01.yco.0000172059.55778.c9
14. Saunders KE, Smith KA. Interventions to prevent self-harm: what does the evidence say? Evid Based Ment Health 2016;19:69-72. https://doi.org/10.1136/eb-2016-102420
15. Carter G, Page A, Large M, Hetrick S, Milner AJ, Bendit N, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guideline for the management of deliberate self-harm. Aust N Z J Psychiatry 2016;50:939-1000. https://doi.org/10.1177/0004867416661039
16. De Leo D, Heller TS. Who are the kids who self-harm? An Australian self-report school survey. Med J Aust 2004;181:140-4.
17. Australian Bureau of Statistics. 3303.0 – Causes of death, Australia, 2016 [Internet]. Canberra: ABS; 2018. http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2016~Main%20Features~Drug%20Induced%20Deaths%20in%20Australia~6 [cited 2019 May 1]
18. Pompili M, Serafini G, Innamorati M, Biondi M, Siracusano A, Di Giannantonio M, et al. Substance abuse and suicide risk among adolescents. Eur Arch Psychiatry Clin Neurosci 2012;262:469-85. https://doi.org/10.1007/s00406-012-0292-0

ARTICLE

Combination psychotropic medicine use in older adults and risk of hip fracture

SUMMARY

Older people might be embarrassed to talk about falling as they worry this may be judged as a loss of their ability to live independently. Ask older patients, at least yearly, if they ever feel unsteady on their feet or if they have fallen.

Consider whether medicines may be contributing to feelings of unsteadiness or falling. Drugs such as benzodiazepines and selective serotonin reuptake inhibitors, particularly if taken together, are associated with a risk of falling and hip fracture.

Review the patient's treatment regimen to see if there are drugs that are no longer required. Psychotropic drugs should usually be tapered gradually so that adverse effects can be minimised.

Involve a range of health professionals to identify and manage the risk of falls. Help patients stay physically active, independent and socially connected.

Kerrie Westaway
Medical writer[1]

Natalie Blacker
Development coordinator[1]

Russell Shute
General practitioner[2]

Rosemary Allin
Pharmacist[3]

Zain Elgebaly
Educational programs support lead[4]

Oliver Frank
Specialist general practitioner,[5] and Senior research fellow[6]

Nicole Pratt
Associate professor,[7] and Lead of evaluation team[1]

Elizabeth Roughead
Professor,[7] and Director[1]

[1] Veterans' Medicines Advice and Therapeutics Education Services (Veterans' MATES) program, Adelaide
[2] Veterans' MATES Clinical Reference Group, Adelaide
[3] Drug and Therapeutics Information Service (DATIS), SA Health, Adelaide
[4] NPS MedicineWise, Sydney
[5] Oakden Medical Centre, Adelaide
[6] Discipline of General Practice, University of Adelaide
[7] Quality Use of Medicines and Pharmacy Research Centre, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide

Keywords
antipsychotics, benzodiazepines, deprescribing, opioids, selective serotonin reuptake inhibitors

Aust Prescr 2019;42:93–6
https://doi.org/10.18773/austprescr.2019.011

Introduction

In Australia, an estimated 30% of people aged over 65 years living in the community and 50% of residents of aged-care facilities fall at least once a year.[1,2] The resultant harm is significant. In 2018, the estimated number of Australians aged 50 years and over who were hospitalised for a hip fracture was 28,000.[3]

An estimated 5% of those who sustain a hip fracture die in hospital, and more than 10% are discharged from hospital to an aged-care facility. More than 50% experience a persistent mobility-related disability one year after their injury.[4]

Falls typically result from multiple interacting factors. The more factors present, the more likely the person is to fall.[1] Medicines are a modifiable risk factor. Adverse effects such as drowsiness, dizziness, blurred vision, confusion or postural hypotension may all contribute to falls.[5,6] The association between psychotropic drugs and the increased risk of hip fracture is well recognised.[7,8] This is likely to be even greater when psychotropic drugs are used in combination.

Psychotropic drugs and hip fracture

Australians are among the highest users of antidepressants in the world, with approximately 10% of the adult population using them each day.[9] Selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat depression. They are often co-prescribed with other drugs, particularly in older people who frequently take multiple medicines to manage multiple morbidities.[5,10] A systematic review and meta-analysis found that depressive symptoms were consistently associated with falls in older people.[11]

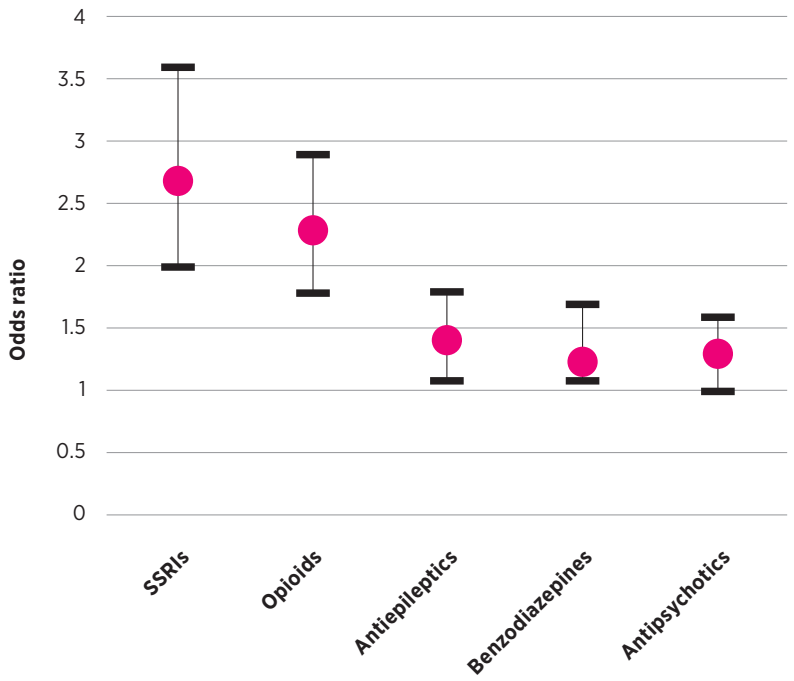
An Australian matched case-control study using data from the Australian Government Department of Veterans' Affairs (DVA) assessed the risk of hip fracture following starting and ongoing use of SSRIs, either alone, or in combination with other psychotropic drugs.[12] The study included 8828 veterans with hip fracture and 35,310 matched controls of the same age and gender, and examined their medicine use in the previous six months. The average age of the cohort was 88 years and 63% were women.[12]

The risk of hip fracture was increased for all five groups of drugs tested (antidepressants, opioids, antiepileptic drugs, benzodiazepines and antipsychotics). The highest risk, more than double, was when SSRIs or opioids were started (see Fig.) and it remained high with ongoing use.[12] International studies have found similar results with SSRIs and opioids.[8,13] Co-administration exacerbated the risks even further.[12]

Starting benzodiazepines and SSRIs together

The highest risk of hip fracture is when a benzodiazepine and an SSRI are started together. There is a fivefold increased risk (odds ratio (OR) = 4.7, 95% confidence interval (CI) 1.7–13) equating to one extra hip fracture for every 17 patients aged 80 years and over who are treated for a year.[12] For

Fig. **Risk of hip fracture associated with starting psychoactive drugs**[12]



Time interval = 180 days
95% confidence interval
SSRI selective serotonin reuptake inhibitor

every 32 people aged 80 years and over who add a benzodiazepine to current SSRI use there will be one extra hip fracture over the year.[12] *

Prescribing a benzodiazepine with an antidepressant to treat anxiety and depression is thought to provide relief from acute symptoms and improve adherence to treatment by reducing the adverse effects of the antidepressant, especially during the first month of treatment.[14,15] However, this combination is not safe in the elderly and a patient's risk of falling should be assessed before prescribing.

Adding opioids to SSRIs

Persistent or chronic pain among older Australians is common and is often associated with depression and anxiety.[16] Adding an opioid for patients already using an SSRI increases the risk of hip fracture, with one extra hip fracture for every 29 patients aged 80 years and over who are treated for a year.[12] There is a need to assess the risk of falls when considering this combination. It may be possible to taper the SSRI in patients who are well, or use an alternative analgesic in older patients who are unsteady on their feet.

Adding antipsychotics to SSRIs

Starting antipsychotic drugs in patients aged 80 years and over who are already using SSRIs results in one extra hip fracture for every 49 patients treated for a year.[12] Antipsychotics and antidepressants are commonly prescribed for elderly people with dementia.[17] However, there is a lack of evidence to show that antidepressants are beneficial in dementia.[18,19] Antipsychotic use in elderly people is associated with adverse effects linked to falling including orthostatic hypotension, confusion and anticholinergic effects.[18,19]

Strategies to reduce the risk of falls

There is a range of interventions that can reduce the risk of falls. A multidisciplinary approach may be helpful.

Review the regimen

Reviewing and modifying older people's medicines to align with their preferences, expectations, treatment goals and level of function is good practice.[20] Gradual withdrawal of psychotropic drugs can reduce falls.[1] When considering which drugs to taper or cease, prioritise them based on their risk and the patient's needs, as well as the ease of dose reduction or cessation, and the availability of safer alternatives. It may be necessary to consult with other prescribers and discuss the options and potential outcomes with the patient.[20] If deprescribing, stop one drug at a time and wean doses slowly over weeks or months while closely monitoring the patient for benefits or adverse effects.[20] Stopping too quickly can cause withdrawal syndromes.

Avoid starting an antidepressant for mild to moderate depression. Psychological management alone is appropriate first-line treatment.[21] For older patients with full resolution of symptoms, consider tapering and ceasing SSRIs. (To find out how to taper and cease an antidepressant, go to: www.veteransmates.net.au/topic-49-therapeutic-brief or www.nps.org.au/australian-prescriber/articles/switching-and-stopping-antidepressants.)

For older patients taking an opioid for chronic pain, consider a multidisciplinary approach to help them understand why pain can persist even after an injury has healed and how active self-management strategies can help them overcome their

* The number needed to harm was calculated from: the odds ratios from Leach et al. 2017[12], hip fracture incidence in the over-80-year-old population in 2016 from the Australian and New Zealand Hip Fracture Registry, Australian over-80-year-old population estimates from the Australian Bureau of Statistics for 2016, and the method of Bjerre and LeLorier 2000.

pain.[22] Review the use of opioids and, where possible, slowly taper and cease or substitute with a non-opioid analgesic as the patient's ability to regain control and self-manage increases. (To find out how to taper and cease an opioid, go to: www.veteransmates.net.au/topic-48-therapeutic-brief.)

In dementia, behavioural and psychological symptoms often fluctuate over time, and occur episodically, most commonly as a result of unmet physical or psychological needs combined with impairment of brain function, and lowered stress thresholds due to the disease process.[23] If an antipsychotic is prescribed for behavioural and psychological symptoms of dementia, limit the dose and duration and also consider the timing of the dose. When possible use non-pharmacological interventions.[23] (To find out how to taper and cease an antipsychotic, go to: www.veteransmates.net.au/topic-44-therapeutic-brief.)

Avoid starting benzodiazepines in older patients. If a benzodiazepine is absolutely necessary, use for a short time only, at a low dose and monitor the patient closely.[24] (For information on how to manage benzodiazepine dependence, and how to taper and cease, go to: www.nps.org.au/news/managing-benzodiazepine-dependence-in-primary-care.)

Discuss risk factors

Encourage patients to work with a range of health professionals to help them stay active and socially connected. Patients at high risk of falling include those who are visually impaired, have cognitive impairment, advanced diabetes or a neurological disease.[1,25] Research suggests that multifactorial interventions that include individual assessment, group or home-based exercise programs, and home safety interventions are effective in helping to reduce falls.[1]

Explain to patients that some medicines can cause adverse effects that might increase their risk of falling. Encourage them to report any dizziness, drowsiness, confusion, or blurred vision. Ask them if they are willing to discuss possible changes to their treatment.

At least once a year and after changes to the treatment regimen, ask older patients if they ever feel unsteady on their feet or if they have fallen. Previous falls increase the risk of subsequent falls.[25] Reassure patients that many things can be done to help prevent falls and to help them stay steady on their feet. A quick and simple falls-risk screen can identify patients who might be at risk of falling.[25] This can be added to the template for a GP Management Plan and for health assessments in patients aged over 75 years.

Being involved in group or home-based exercise classes that focus on improving balance and building strength can reduce the risk of falls. It can also help to prevent injuries resulting from a fall.[1]

In Australia, one in four men and two in five women aged 50 years and over sustain a minimal trauma fracture, most commonly because of osteoporosis or osteopenia.[26] Identify patients, without a history of a previous fracture, who are at high risk of poor bone health and refer them for a bone mineral density scan. There is a Medicare subsidy for bone mineral densitometry for people over 70 years who have not had a bone mineral density scan before and for younger people with specific risk factors for osteoporosis.[27]

Allied health interventions

Interventions by an occupational therapist to improve home safety can be effective particularly if the patient is at high risk of falling. (To find an occupational therapist, go to: www.otaus.com.au/find-an-occupational-therapist.)

An assessment of foot pain by a podiatrist and advice about appropriate footwear, ankle and foot exercises, customised insoles and falls prevention strategies can help to reduce the risk of falling.[1,25] DVA funds podiatry services for eligible DVA patients. (To find a podiatrist, go to: www.podiatry.org.au/find-a-podiatrist.)

Encourage patients to have their eyesight checked every two years or more often if needed.[23] Remind patients that eye drops or eye ointment can cause blurred vision which can increase their risk of falling.

Conclusion

Psychotropic drugs increase the risk of falls. SSRIs, used alone or concurrently with benzodiazepines, opioids or antipsychotic drugs, significantly increase the risk of hip fracture and in many elderly patients they may pose an unacceptable risk. The degree to which the risk is increased following concurrent use of these drugs might not be well recognised. Asking patients about whether they have previously fallen and reviewing their medicines can help to reduce their risk. ◁

Conflict of interest: none declared

Acknowledgement: This article is adapted and reproduced from the Veterans' MATES Therapeutic Brief, Medicines: the hidden contributor to falls and hip fracture. The Australian Government Department of Veterans' Affairs Veterans' MATES Program is provided

Q:

SELF-TEST QUESTIONS

True or false?

1. Opioids increase the risk of hip fractures.
2. During the first few weeks of therapy with a selective serotonin reuptake inhibitor a benzodiazepine can reduce the risk of falls.

Answers on page 113

by the Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, University of South Australia, in association with Discipline of General Practice, University of Adelaide; Discipline of Public Health, University of Adelaide; NPS MedicineWise; Australian Medicines Handbook; and Drug and Therapeutics Information Service. Veterans' MATES Program materials are available at: www.veteransmates.net.au.

REFERENCES

1. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012:CD007146. https://doi.org/10.1002/14651858.CD007146.pub3
2. Australian Commission on Safety and Quality in Health Care. Preventing falls and harms from falls in older people: best practice guidelines for Australian residential aged care facilities. Sydney: ACSQHC; 2009. https://www.safetyandquality.gov.au/publications/preventing-falls-and-harm-from-falls-in-older-people-best-practice-guidelines-for-australian-residential-aged-care-facilities-2009 [cited 2019 May 1]
3. Watts JW, Abimanyi-Ochom J, Sanders KM. Osteoporosis costing all Australians: a new burden of disease analysis – 2012 to 2022. Sydney: Osteoporosis Australia; 2013. https://www.osteoporosis.org.au/research-position-papers [cited 2019 May 1]
4. ANZHFR bi-national annual report for hip fracture care 2017. Australian and New Zealand Hip Fracture Registry; 2017. https://anzhfr.org/2017-annual-report [cited 2019 May 1]
5. Leach M, Pratt N, Roughead E. Medicine use among older Australians before and after hip fracture. J Pharm Pract Res 2013;43:265-8. https://doi.org/10.1002/j.2055-2335.2013.tb00271.x
6. Takkouche B, Montes-Martínez A, Gill SS, Etminan M. Psychotropic medicines and the risk of fracture. Drug Saf 2007;30:171-84. https://doi.org/10.2165/00002018-200730020-00006
7. Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people: a review of the evidence. CNS Drugs 2003;17:825-37. https://doi.org/10.2165/00023210-200317110-00004
8. Wu Q, Bencaz AF, Hentz JG, Crowell MD. Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case-control studies. Osteoporos Int 2012;23:365-75. https://doi.org/10.1007/s00198-011-1778-8
9. Davey CG, Chanen AM. The unfulfilled promise of the antidepressant medications. Med J Aust 2016;204:348-50. https://doi.org/10.5694/mja16.00194
10. Caughey GE, Roughead EE, Shakib S, McDermott RA, Vitry AI, Gilbert AL. Comorbidity of chronic disease and potential treatment conflicts in older people dispensed antidepressants. Age Ageing 2010;39:488-94. https://doi.org/10.1093/ageing/afq055
11. Kvelde T, McVeigh C, Toson B, Greenaway M, Lord SR, Delbaere K, et al. Depressive symptomatology as a risk factor for falls in older people: systematic review and meta-analysis. J Am Geriatr Soc 2013;61:694-706. https://doi.org/10.1111/jgs.12209
12. Leach MJ, Pratt NL, Roughead EE. Risk of hip fracture in older people using selective serotonin reuptake inhibitors and other psychoactive medicines concurrently: a matched case-control study in Australia. Drugs Real World Outcomes 2017;4:87-96. https://doi.org/10.1007/s40801-017-0107-8
13. Kuschel BM, Laflamme L, Möller J. The risk of fall injury in relation to commonly prescribed medications among older people--a Swedish case-control study. Eur J Public Health 2015;25:527-32. https://doi.org/10.1093/eurpub/cku120
14. Furukawa TA, Streiner DL, Young LT, Kinoshita Y. Antidepressant plus benzodiazepine for major depression. Cochrane Database Syst Rev 2001:CD001026. https://doi.org/10.1002/14651858.CD001026
15. Pfeiffer PN, Ganoczy D, Zivin K, Valenstein M. Benzodiazepines and adequacy of initial antidepressant treatment for depression. J Clin Psychopharmacol 2011;31:360-4. https://doi.org/10.1097/JCP.0b013e318217b4c4
16. Henderson JV, Harrison CM, Britt HC, Bayram CF, Miller GC. Prevalence, causes, severity, impact, and management of chronic pain in Australian general practice patients. Pain Med 2013;14:1346-61. https://doi.org/10.1111/pme.12195
17. Moyle W, El Saifi N, Draper B, Jones C, Beattie E, Shum D, et al. Pharmacotherapy of persons with dementia in long-term care in Australia: a descriptive audit of central nervous system medications. Curr Drug Saf 2017;12:95-102. https://doi.org/10.2174/1574886312666170209113203
18. Farina N, Morrell L, Banerjee S. What is the therapeutic value of antidepressants in dementia? A narrative review. Int J Geriatr Psychiatry 2017;32:32-49. https://doi.org/10.1002/gps.4566
19. Orgeta V, Tabet N, Nilforooshan R, Howard R. Efficacy of antidepressants for depression in Alzheimer's disease: systematic review and meta-analysis. J Alzheimers Dis 2017;58:725-33. https://doi.org/10.3233/JAD-161247
20. Le Couteur D, Banks E, Gnjidic D, McLachlan A. Deprescribing. Aust Prescr 2011;34:182-5. https://doi.org/10.18773/austprescr.2011.095
21. Malhi GS, Outhred T, Hamilton A, Boyce PM, Bryant R, Fitzgerald PB, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: major depression summary. Med J Aust 2018;208:175-80. https://doi.org/10.5694/mja17.00659
22. Royal Australasian College of Physicians. Prescription opioid policy: improving mangement of chronic non-malignant pain and prevention of problems associated with prescription opioid use. Sydney: RACP; 2009. https://www.ranzcp.org/files/resources/college_statements/practice_guidelines/chronic-non-malignant-pain-2009.aspx [cited 2019 May 1]
23. Burns K, Jayasinha R, Brodaty H. A clinican's field guide to good practice: managing behavioural and pyschological symptoms of dementia. Sydney: Dementia Collaboratve Research Centres – Assessment and Better Care; 2014. http://www.dementiaresearch.org.au/index.php?option=com_dcrc&view=dcrc&layout=project&Itemid=112&research_topic=0&researcher=77&research_type=0&year=0&population=0&centre=1&keywords=&searchtype=EXACT&recruiting_location_id=0&pid=260&search=true [cited 2019 May 1]
24. Prescribing drugs of dependence in general practice, Part B: benzodiazepines. Melbourne: The Royal Australian College of General Practitioners; 2015. www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/prescribing-drugs-of-dependence/prescribing-drugs-of-dependence-part-b [cited 2019 May 1]
25. Australian Commission on Safety and Quality in Healthcare. Preventing falls and harms from falls in older people. Best practice guidelines for Australian community care. Sydney: ACSQH; 2009. [PDF] https://www.safetyandquality.gov.au/wp-content/uploads/2012/01/Guidelines-RACF.pdf [cited 2019 May 1]
26. Australian Insitute of Health and Welfare. Estimating the prevalence of osteoporosis in Australia. Canberra: AIHW; 2014. www.aihw.gov.au/reports/arthritis-other-musculoskeletal-conditions/estimating-the-prevalence-of-osteoporosis-in-austr/contents/table-of-contents [cited 2019 May 1]
27. Australian Government Department of Health. Medicare Benefits Schedule – Item 12306. Category 2 – diagnostic procedures and investigations. Bone densitometry. www9.health.gov.au/mbs/fullDisplay.cfm?type=item&qt=ItemID&q=12306 [cited 2019 May 1]

Australian Prescriber
VOLUME 42 : NUMBER 3 : JUNE 2019

ARTICLE

Immunomodulatory drugs in pregnancy and lactation

SUMMARY

Pregnancy presents challenges for women with autoimmune diseases. It is associated with significant physiological, hormonal and immunomodulatory changes which are complex and vary according to the stage of pregnancy.

Pregnancy planning and counselling should be offered.

Autoimmune diseases such as rheumatoid arthritis tend to improve in pregnancy while systemic lupus erythematosus may increase in activity.

During pregnancy the chosen regimen should control or prevent underlying disease activity and minimise risk to the fetus. Ideally, women should be on a stable regimen before conception.

Poorly controlled disease is associated with poor outcomes for both mother and fetus, such as higher risks of pre-eclampsia, early delivery and growth restriction of the fetus.

Postpartum, there is a sudden fall in hormone concentrations, and a switch to a pro-inflammatory state. This increases the risk of relapse of many autoimmune diseases in particular rheumatoid arthritis, Crohn's disease and autoimmune hepatitis.

Many drugs are compatible with breastfeeding, but there are limited data on many of the new drugs.

Kathy Paizis
Obstetric medicine physician and Nephrologist, Mercy Hospital for Women, Western Health Sunshine, Austin Health, Melbourne

Keywords
rheumatoid arthritis, systemic lupus erythematosis, teratogens

Aust Prescr 2019;42:97–101
https://doi.org/10.18773/austprescr.2019.026

Introduction

Many autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus are more frequent in women than in men. These diseases are likely to occur during the childbearing years.

There are physiological, hormonal and immunomodulatory changes during pregnancy. Diseases with T helper type 1 phenotypes (rheumatoid arthritis) may improve with pregnancy while T helper type 2 phenotypes (such as systemic lupus erythematosus) may flare in pregnancy.

Poorly controlled disease is associated with adverse pregnancy outcomes such as miscarriages, pre-eclampsia, growth restriction and early delivery. There are also specific maternal risks associated with the underlying disease. Pregnancy should ideally be managed by a multidisciplinary team including obstetricians, obstetric medical physicians and rheumatologists.

The Australian categorisation of drugs in pregnancy is an assessment of the risk of harm. While the categories A, B, C, D and X are a guide to the level of risk if a drug is taken during pregnancy, the system has its limitations.[1] For example, category D drugs may increase the incidence of fetal malformations but may still be needed to keep control of an autoimmune condition during pregnancy. Although they are both in category D, hydroxychloroquine has been used in pregnancy while methotrexate must be avoided.

Hormone concentrations drop rapidly postpartum and there is a switch to a pro-inflammatory state. These changes increase the risk of relapse in diseases such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus and autoimmune hepatitis.

There are potential risks to the baby from the drugs if they pass into breast milk. Often only small amounts are found so the drugs are compatible with breastfeeding. However, safety data are limited for some drugs and breastfeeding is not recommended if the mother is taking drugs such as methotrexate or mycophenolate.

Pregnancy planning

Pregnancy planning should be offered to all women of childbearing age who have an autoimmune disease. This should include education on contraception to avoid unplanned pregnancies. Pregnancy is contraindicated if the disease is poorly controlled and if the woman is taking teratogenic drugs such as methotrexate, mycophenolate or leflunomide.

Planning enables a switch to drugs that help control or prevent the activity of the disease while minimising risks to the fetus. This switch should ideally take place before conception.

Contraception

Contraceptive counselling is essential in women with rheumatic diseases, but is often overlooked. The choice of contraception is dependent on the severity of the disease and organ involvement, use of teratogenic drugs, underlying risk factors such as thrombotic risk, the presence of hypertension and often social circumstances.

The most effective forms of contraception are progestogen intrauterine devices (IUDs) and progestogen implants. These methods have failure rates of less than 1% per year and efficacy does not rely on adherence. There is often reluctance to use IUDs in women taking immunosuppressive drugs due to a fear of an increased risk of pelvic infections and a possible decrease in contraceptive efficacy. Data regarding the use of IUDs in immunosuppressed women are limited, but international guidelines do not consider immunosuppressive drugs to be a contraindication.[2,3] IUDs are an acceptable form of contraception for both multiparous and nulliparous women.[3]

Progestogen implants have been associated with abnormal bleeding, but discontinuation rates are low. IUDs and progestogen implants have not been associated with an increased thrombotic risk and can safely be used in women with a history of thrombosis.

The efficacy of the combined oral contraceptive pill is user dependent with failure rates up to 9% per year as most women do not follow the strict criteria for use. A low-dose oral contraceptive pill has not been associated with increased flares in women with stable lupus. Contraindications include women more than 40 years of age, difficult to control hypertension, history of thrombosis, including conditions with increased thrombotic risk (antiphospholipid syndrome), and liver disease.

Corticosteroids

Corticosteroids are the most frequently used drugs for autoimmune diseases. They are safe in all trimesters of pregnancy (category A). Prednisolone is the preferred steroid as it is metabolised by the placenta with 10% of the maternal dose reaching the fetus.

Epidemiological studies have associated first trimester steroid use with cleft palate,[4] but recent data have not confirmed this.[5,6] Other reports regarding premature delivery and growth restriction have also not been reproducible.[7] Steroids are associated with increased risks of hypertension, gestational diabetes, osteopenia and infections. These effects are dose dependent. Recent observational data show an incremental risk of serious infections with high-dose steroids. The incidence of infection with low-dose steroids (<10 mg) was reassuringly low.[8] Screening for gestational diabetes should be performed at 16 and 28 weeks with a glucose tolerance test.

In women requiring prednisolone more than 10 mg daily, consideration should be given to the addition of disease-modifying antirheumatic drugs (hydroxychloroquine, sulfasalazine, tumour necrosis factor inhibitors, azathioprine). This may help to improve disease control and decrease adverse pregnancy outcomes. High-dose steroids should not be withheld in women with uncontrolled disease activity. In women on long-term steroids, stress doses of intravenous steroids during labour are required.

Small amounts of steroids are found in breast milk, but they are compatible with breastfeeding. In women on higher doses of steroids (more than 20 mg prednisolone) delaying feeds for 3–4 hours after a dose can further decrease the baby's exposure to the drug.

Azathioprine and mercaptopurine

Azathioprine is commonly used in the management of transplantation, lupus nephritis, inflammatory bowel disease and autoimmune hepatitis. It is converted to mercaptopurine (6-MP) which is then enzymatically broken down to active metabolites known as thioguanines.

Despite the fact that azathioprine has not been found to be a human teratogen, it is listed as a category D drug. Doses below 2 mg/kg have not been associated with an increased risk of congenital malformations (over 1300 pregnancies), stillbirth and miscarriages.[9,10] There have been links to premature delivery and intrauterine growth restriction, but this may be due to the severity of the underlying disease rather than the drug.[11]

If azathioprine is started in pregnancy, the activity of the enzyme thiopurine S-methyltransferase (TPMT) should be measured. Decreased activity is associated with a high risk of potentially fatal bone marrow toxicity. High-dose folic acid (5 mg) is used in combination with azathioprine and mercaptopurine to prevent antifolate effects.

Azathioprine is compatible with breastfeeding as very small amounts are excreted in breast milk. The highest concentrations are found in breast milk 1–2 hours after drug ingestion.[12]

Mycophenolate

Mycophenolate is a very effective immunosuppressant for many autoimmune diseases in non-pregnant women. While it is classified as category D, mycophenolate is teratogenic. It should be stopped at least six weeks before conception.

There have been consistent data supporting evidence of mycophenolate embryopathy. Typical malformations include cleft lip and palate, congenital heart defects, diaphragmatic hernia, shortened fingers, and ear, eye and renal abnormalities.[13,14] Mycophenolate has also been associated with high rates of miscarriage.[13]

Breastfeeding is not recommended as there are limited data.

To date registry data have not shown an increased incidence of malformations in babies whose fathers took mycophenolate. Counselling these men is recommended with regards to the harm versus benefit of stopping mycophenolate when planning pregnancy with their partners.[15]

Hydroxychloroquine

Hydroxychloroquine is used in the management of lupus and other rheumatological conditions. It has immunomodulatory activity as well as antithrombotic, antiangiogenic and antilipidaemic actions.[16] Although hydroxychloroquine is a category D drug, there are now over 821 case reports of pregnancies with no increase in congenital malformations, miscarriage or stillbirth.[9]

Hydroxychloroquine has been associated with a decrease in flares of lupus during pregnancy and may limit the need for high-dose steroids. Observational studies have shown a decrease in the incidence of fetal heart block and cardiomyopathy in Ro antibody-positive women. In addition, hydroxychloroquine has been linked to a reduction in growth restriction and may have antithrombotic effects in women with antiphospholipid syndrome. Hydroxychloroquine should be continued in pregnancy for women with lupus and those requiring treatment for rheumatic disease.[17]

Hydroxychloroquine is found at low concentrations in breast milk. It is compatible with breastfeeding.[10]

Methotrexate

Methotrexate has many indications including rheumatological conditions – psoriatic arthritis, vasculitis and rheumatoid arthritis. It is a folic acid antagonist.[18]

Despite being a teratogen, methotrexate is a category D drug. It has been associated with a high miscarriage rate (42%) and a specific pattern of malformations and congenital heart defects (10%).[19] The timing and dosing of methotrexate may influence adverse outcomes. Recent observational data in women exposed to doses of methotrexate less than 30 mg after conception showed a 6.6% risk of major malformations and a miscarriage rate of 20%.[19] Women using less than 30 mg methotrexate per week in the three months before conception did not have an increased risk of congenital malformations or miscarriage.[19] It is currently recommended that methotrexate be stopped three months before conception. If it is taken within three months of conception, 5 mg folic acid is recommended until at least 12 weeks of gestation, because of methotrexate's antifolate activity.

Breastfeeding is not recommended as there are insufficient data in lactation.

Paternal exposure

It is recommended that men stop methotrexate three months before conception. Two recent observational studies did not find an increased risk of congenital malformations when methotrexate (<30 mg) was used 90 days before conception.[20,21] Condoms are not required during pregnancy. Counselling men who wish to father children about the harm–benefit ratio of stopping methotrexate is advised.

Sulfasalazine and mesalazine

Sulfasalazine is often indicated for rheumatoid arthritis. Mesalazine and sulfasalazine are used in the management of inflammatory bowel disease. Sulfasalazine is category A while mesalazine is category C. These drugs have been used in pregnancy and were not associated with an increased risk of congenital malformations, miscarriage, growth restriction or prematurity.[10] There is a theoretical risk that sulfasalazine may cause folic acid deficiency as it inhibits dihydrofolate reductase and folate uptake into the cell. High-dose folic acid (5 mg) is recommended for at least one month pre-conception and up to 12 weeks after conception.[18]

Sulfasalazine and mesalazine are safe to use in breastfeeding. They should be used with caution if the baby is premature and has jaundice.[10]

Paternal exposure

Sulfasalazine and mesalazine are associated with decreased fertility in men, but not women. They decrease sperm counts and motility, but sperm counts usually return to normal two months after stopping the drug.[22,23]

Calcineurin inhibitors

Ciclosporin and tacrolimus have been used in the management of lupus nephritis. Tacrolimus has a more preferable adverse effect profile as it does not cause hirsutism.

Calcineurin inhibitors are not teratogenic. Although tacrolimus has been associated with a higher miscarriage rate, small for gestational age and premature delivery, this may be confounded by

the severity of the underlying disease.[10] Calcineurin inhibitors are associated with higher rates of hypertension and diabetes, so a glucose tolerance test at 16 and 28 weeks is recommended.[24]

Drug concentrations need to be closely monitored as they can change in pregnancy due to increased drug clearance, increased volume of distribution and less protein binding of the drug. Standard assays measure total tacrolimus concentrations and do not differentiate between unbound (free and active) versus bound drug. It is therefore recommended that concentrations are maintained at the lower end of the therapeutic range.[25]

Women taking calcineurin inhibitors can breastfeed. Small amounts are found in breast milk, but no harmful effects have been reported.[10]

Leflunomide

Leflunomide interferes with RNA and DNA synthesis, but limited data have not shown an increased risk in congenital malformations in humans. In view of its potential risk leflunomide is considered unsafe in pregnancy (category X).[9,10] Discontinuation of leflunomide before conception is insufficient for drug elimination as metabolites can be present for up to 48 months.[26] Women on leflunomide before conception (48 months) or in early pregnancy should therefore undergo a colestyramine washout (8 g orally three times daily for 11 days) until drug concentrations are less than 0.02 mg/L. Additional colestyramine is indicated if concentrations are above 0.02 mg/L.

Tumour necrosis factor alpha inhibitors

Tumour necrosis factor alpha (TNF) inhibitors are commonly used in the management of inflammatory bowel disease, rheumatoid arthritis, seronegative and psoriatic arthritis. Registry data, case series and cohort analysis have not shown an increase in congenital malformations. Experience is greater with infliximab (>1200 cases), etanercept (>600 cases), adalimumab (>400) and certolizumab (>370). Data are limited on golimumab.[10,27,28] Most of the class are considered to be category C drugs.

The decision to continue biological therapies in pregnancy is dependent on underlying disease severity as poorly controlled disease is associated with a higher risk of adverse outcomes for mother and fetus.

The TNF inhibitors differ significantly in their molecular structure, size and half-life. Infliximab and adalimumab are IgG1 molecules, etanercept is a fusion molecule of IgG1, and certolizumab is a pegylated molecule that lacks the Fc domain. All IgG molecules are actively transported across the placenta via the Fc receptor, IgG1 being most efficiently transferred. This transfer is therefore highest for infliximab and adalimumab, low for etanercept and extremely low for certolizumab (diffusion rather than active transport) as it lacks the Fc domain. Placental transfer begins at 14 weeks and increases to delivery with maximal transfer in the last four weeks of pregnancy.[29,30]

To ensure no or low concentrations of the drug in cord blood it is recommended that infliximab be ceased at 18 weeks. Adalimumab should be ceased at 30–32 weeks. Etanercept and in particular certolizumab can be continued until delivery as minimal amounts are transferred to the fetus. In cases where disease activity precludes cessation of infliximab or adalimumab it is recommended that treatment be continued until delivery.[10,28]

There are limited, but reassuring data on breastfeeding. Small amounts are found in breast milk, but these molecules are large and absorption is thought to be minimal.[10] Avoid live vaccines (rotavirus) for the first six months in newborns if a TNF inhibitor is continued in the third trimester.[27] Measles-mumps-rubella vaccine is safe to be given at 12 months.

Paternal exposure to a TNF inhibitor has not been associated with adverse effects on offspring.

Rituximab

Rituximab is an antibody used in the management of antineutrophilic cytoplasmic antibody vasculitis, resistant rheumatoid arthritis and in resistant systemic lupus erythematosus. It is a category C drug. The timing of rituximab exposure during pregnancy has to be taken into account when assessing risk as it is an IgG1 molecule. First trimester use has been associated with an increased risk of miscarriages (potentially due to underlying disease) with no increased risk in malformations. There have been 23 reported cases of rituximab use in the second and third trimester (risk of fetal transfer) with no reports of congenital malformations or adverse fetal or maternal outcomes. However, there was a 30% incidence of cytopenias in the newborn. It is recommended that rituximab be replaced or ceased six months before conception.[28]

There are limited data on breastfeeding. The pharmacological properties of rituximab suggest it should be safe.[9,10,27]

Conclusion

Women with underlying autoimmune disease should receive pre-pregnancy counselling. This includes advice on contraception, and often a switch to drugs that control disease and minimise harm to the fetus.

Active disease in pregnancy is associated with adverse pregnancy outcomes. Breastfeeding is often possible. Close postpartum follow-up is important as many autoimmune diseases can flare during this period. ◀

Kathy Paizis has done research funded by UCB Australia (manufacturer of certolizumab).

REFERENCES

1. Kennedy D. Classifying drugs in pregnancy. Aust Prescr 2014;37:38-40. https://doi.org/10.18773/austprescr.2014.018
2. Stringer EM, Kaseba C, Levy J, Sinkala M, Goldenberg RL, Chi BH, et al. A randomized trial of the intrauterine contraceptive device vs hormonal contraception in women who are infected with the human immunodeficiency virus. Am J Obstet Gynecol 2007;197:144.e1-8. https://doi.org/10.1016/j.ajog.2007.03.031
3. Curtis KM, Tepper NK, Jatlaoui TC, Berry-Bibee E, Horton LG, Zapata LB, et al. US medical eligibility criteria for contraceptive use, 2016. MMWR Recomm Rep 2016;65:1-104. http://dx.doi.org/10.15585/mmwr.mm6637a6
4. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000;62:385-92. https://doi.org/10.1002/1096-9926(200012)62:6<385::AID-TERA5>3.0.CO;2-Z
5. Hviid A, Mølgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. CMAJ 2011;183:796-804. https://doi.org/10.1503/cmaj.101063
6. Bay Bjørn AM, Ehrenstein V, Hundborg HH, Nohr EA, Sørensen HT, Nørgaard M. Use of corticosteroids in early pregnancy is not associated with risk of oral clefts and other congenital malformations in offspring. Am J Ther 2014;21:73-80. https://doi.org/10.1097/MJT.0b013e3182491e02
7. Al Arfaj AS, Khalil N. Pregnancy outcome in 396 pregnancies in patients with SLE in Saudi Arabia. Lupus 2010;19:1665-73. https://doi.org/10.1177/0961203310378669
8. Desai RJ, Bateman BT, Huybrechts KF, Patorno E, Hernandez-Diaz S, Park Y, et al. Risk of serious infections associated with use of immunosuppressive agents in pregnant women with autoimmune inflammatory conditions: cohort study. BMJ 2017;356:j895. https://doi.org/10.1136/bmj.j895
9. Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, et al.; BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford) 2016;55:1693-7. https://doi.org/10.1093/rheumatology/kev404
10. Götestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 2016;75:795-810. https://doi.org/10.1136/annrheumdis-2015-208840
11. Cleary BJ, Källén B. Early pregnancy azathioprine use and pregnancy outcomes. Birth Defects Res A Clin Mol Teratol 2009;85:647-54. https://doi.org/10.1002/bdra.20583
12. Sau A, Clarke S, Bass J, Kaiser A, Marinaki A, Nelson-Piercy C. Azathioprine and breastfeeding: is it safe? BJOG 2007;114:498-501. https://doi.org/10.1111/j.1471-0528.2006.01232.x
13. Sifontis NM, Coscia LA, Constantinescu S, Lavelanet AF, Moritz MJ, Armenti VT. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation 2006;82:1698-702. https://doi.org/10.1097/01.tp.0000252683.74584.29
14. Hoeltzenbein M, Elefant E, Vial T, Finkel-Pekarsky V, Stephens S, Clementi M, et al. Teratogenicity of mycophenolate confirmed in a prospective study of the European Network of Teratology Information Services. Am J Med Genet A 2012;158A:588-96. https://doi.org/10.1002/ajmg.a.35223
15. Lopez-Lopez I, Rodelo-Haad C, Agüera ML, Cabello-Jabalquinto R, Esquivias-Motta E, Navarro MD, et al. Administration of mycophenolic acid is not associated with malformations in descendants from kidney transplanted males. PLoS One 2018;13:e0202589. https://doi.org/10.1371/journal.pone.0202589
16. Wallace DJ, Gudsoorkar VS, Weisman MH, Venuturupalli SR. New insights into mechanisms of therapeutic effects of antimalarial agents in SLE. Nat Rev Rheumatol 2012;8:522-33. https://doi.org/10.1038/nrrheum.2012.106
17. Knight CL, Nelson-Piercy C. Management of systemic lupus erythematosus during pregnancy: challenges and solutions. Open Access Rheumatol 2017;9:37-53. https://doi.org/10.2147/OARRR.S87828
18. Hernández-Díaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med 2000;343:1608-14. https://doi.org/10.1056/NEJM200011303432204
19. Weber-Schoendorfer C. Chambers C, Wacker E, Beghin D, Bernard N, Shechtman S, et la. Pregnancy outcome after methotrexate treatment for rheumatic disease prior to or during early pregnancy: a prospective multicenter cohort study. Arthritis Rheumatol 2014;66:1101-10. https://doi.org/10.1002/art.38368
20. Weber-Schoendorfer C, Hoeltzenbein M, Wacker E, Meister R, Schaefer C. No evidence for an increased risk of adverse pregnancy outcome after paternal low-dose methotrexate: an observational cohort study. Rheumatology (Oxford) 2014;53:757-63. https://doi.org/10.1093/rheumatology/ket390
21. Eck LK, Jensen TB, Mastrogiannis D, Torp-Pedersen A, Askaa B, Nielsen TK, et al. Risk of adverse pregnancy outcome after paternal exposure to methotrexate within 90 days before pregnancy. Obstet Gynecol 2017;129:707-14. https://doi.org/10.1097/AOG.0000000000001936
22. O'Moráin C, Smethurst P, Doré CJ, Levi AJ. Reversible male infertility due to sulphasalazine: studies in man and rat. Gut 1984;25:1078-84. https://doi.org/10.1136/gut.25.10.1078
23. Shin T, Kobori Y, Suzuki K, Iwahata T, Yagi H, Soh S, et al. Inflammatory bowel disease in subfertile men and the effect of mesalazine on fertility. Syst Biol Reprod Med 2014;60:373-6. https://doi.org/10.3109/19396368.2014.952391
24. Chakkera HA, Kudva Y, Kaplan B. Calcineurin inhibitors: pharmacologic mechanisms impacting both insulin resistance and insulin secretion leading to glucose dysregulation and diabetes mellitus. Clin Pharmacol Ther 2017;101:114-20. https://doi.org/10.1002/cpt.546
25. Zheng S, Easterling TR, Umans JG, Miodovnik M, Calamia JC, Thummel KE, et al. Pharmacokinetics of tacrolimus during pregnancy. Ther Drug Monit 2012;34:660-70. https://doi.org/10.1097/FTD.0b013e3182708edf
26. Østensen M, Khamashta M, Lockshin M, Parke A, Brucato A, Carp H, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther 2006;8:209. https://doi.org/10.1186/ar1957
27. Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R, Llurba E, Gris JM. Tumour necrosis factor-alpha and pregnancy: focus on biologics. An updated and comprehensive review. Clin Rev Allergy Immunol 2017;53:40-53. https://doi.org/10.1007/s12016-016-8596-x
28. Gerosa M, Argolini LM, Artusi C, Chighizola CB. The use of biologics and small molecules in pregnant patients with rheumatic diseases. Expert Rev Clin Pharmacol 2018;11:987-98. https://doi.org/10.1080/17512433.2018.1525293
29. Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. Am J Gastroenterol 2009;104:228-33. https://doi.org/10.1038/ajg.2008.71
30. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. Am J Reprod Immunol 1996;36:248-55. https://doi.org/10.1111/j.1600-0897.1996.tb00172.x

SELF-TEST QUESTIONS

True or false?

3. A weekly dose of methotrexate to control rheumatoid arthritis can continue until the third trimester of pregnancy.

4. Calcineurin inhibitors, such as ciclosporin, should be stopped at least three months before a planned pregnancy.

Answers on page 113

NEW DRUGS

New drugs

Aust Prescr 2019;42:102
https://doi.org/10.18773/austprescr.2019.029
First published 24 April 2019

Cerliponase alfa

Approved indication: neuronal ceroid lipofuscinosis type 2 disease

Brineura (BioMarin)
vials containing 150 mg/5 mL solution
Australian Medicines Handbook Appendix A

The lysosomal storage diseases result from inborn errors of metabolism. Enzyme deficiencies cause an accumulation of substrates inside lysosomes. Neuronal ceroid lipofuscinosis (Batten disease) results from the accumulation of lipofuscin. In the type 2 form of the disease there is a deficiency of the enzyme tripeptidyl peptidase due to an autosomal recessive genetic defect.

The disease causes developmental delay when children are 2–4 years old. This is followed by seizures and loss of vision with death usually occurring in adolescence.

Cerliponase alfa is a recombinant form of the deficient enzyme and is activated in the lysosomes. It has to be given by intracerebroventricular infusion. This requires the surgical implantation of a reservoir and catheter. The infusion is given over several hours every other week. After the infusion, the device is cleared with a flushing solution. The half-life of cerliponase alfa in cerebrospinal fluid is about seven hours and the enzyme is probably cleared by hydrolysis.

Neuronal ceroid lipofuscinosis type 2 is a rare disease so there is a limited number of children to participate in clinical trials. The main study of cerliponase alfa was an open-label trial of 23 patients with a mean age of five years. They were treated for up to 48 weeks and, depending on their response, could continue in an extension study. The mean duration of treatment at the recommended dose was 115 weeks.

There was no control group, so the outcomes of the trial had to be compared with historical cases. The main outcome was a 2-point decline in a clinical rating scale assessing motor and language skills (range 0–6 points). This decline occurred after a median of 49 weeks in the historical controls, but by that time only 9% of the intervention group had experienced this decline. Over 48 weeks the rate of decline was 2.12 points in the controls, but only 0.27 points with cerliponase alfa.[1]

Adverse events were very common, but some, such as seizures, could be due to the disease itself. No child stopped treatment because of adverse events. Several events, such as some infections, were related to the device or the infusion. As hypersensitivity is common, antihistamines are recommended 30–60 minutes before the infusion. Vomiting and fever are also common.[1]

The trial showed that children treated with cerliponase alfa are significantly less likely to have a decline in motor and language scores than historical controls. Although it is still significant, the difference in the rate of decline narrows (2.06 vs 0.38 points) once the results are adjusted for covariates such as age. Cerliponase alfa may slow the decline, but it does not stop the loss of brain cells as MRI showed decreasing grey matter in the treated children.[1] Longer term follow-up will be needed to see if cerliponase alfa prevents blindness or improves quality of life and survival.

T T manufacturer provided additional useful information

REFERENCE

1. Schulz A, Ajayi T, Specchio N, de Los Reyes E, Gissen P, Ballon D, et al. Study of intraventricular cerliponase alfa for CLN2 disease. N Engl J Med 2018;378:1898-907. https://doi.org/10.1056/NEJMoa1712649

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.

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.

Durvalumab

Aust Prescr 2019;42:103–4
https://doi.org/10.18773/austprescr.2019.030
First published 24 April 2019

Approved indications: urothelial carcinoma, non-small cell lung cancer

Imfinzi (AstraZeneca)
vials containing 120 mg or 500 mg concentrate for dilution
Australian Medicines Handbook section 14.2.1, Antineoplastic antibodies

Some tumours evade detection by the immune system by expressing a molecule called programmed cell death ligand 1 (PD-L1). This interacts with the programmed cell death 1 (PD-1) receptor on the surface of T cells to suppress the immune response. Inhibiting these immune checkpoints therefore enables the T cells to recognise the tumour cells and attack them. Immune checkpoint inhibitors are being used in a variety of cancers including melanoma, non-small cell lung cancer and urothelial carcinoma.[1]

Durvalumab is a genetically engineered monoclonal antibody to PD-L1. It blocks the interaction of PD-L1 and PD-1, enabling T-cell activation.

The antibody concentrate is diluted then infused intravenously over an hour every two weeks. A steady state is reached after 16 weeks. The antibody is cleared with a half-life of 18 days. No dose adjustment is needed for renal or hepatic impairment, but durvalumab has not been studied in patients with severe kidney impairment.

In urothelial cancer durvalumab is being studied as a second-line drug. A phase I/II trial enrolled patients with inoperable or metastatic transitional-cell bladder carcinoma who had progressed on, or been ineligible for, other therapies. In a group of 61 patients 19 had received three or more previous therapies. After a median follow-up of 4.3 months there was an objective response in 13 patients (based on the RECIST criteria). The response rate was highest in patients with tumours expressing PD-L1.[2]

A later report on the same trial evaluated 191 patients with a median follow-up of 5.8 months. There were 34 objective responses including seven complete responses. Again, the response rates were higher in patients with greater PD-L1 expression. The median progression-free survival was 1.5 months. Although the data are incomplete, overall survival was 20 months in those with high PD-L1 expression and 8.1 months in other patients.[3] As almost all the patients had been previously treated with carboplatin or cisplatin, the Australian approval of durvalumab specifies that there must have been disease progression during or following platinum-containing chemotherapy.

For non-small cell lung cancer, durvalumab has been studied in a phase III trial. The patients had unresectable, locally advanced cancer (Stage III) and had been treated with chemotherapy and radiation. Infusions of durvalumab were given to 473 patients and 236 were given a placebo. After a median follow-up of 14.5 months there was an objective response in 28.4% of the durvalumab group and 16% of the placebo group. There was a significant difference in progression-free survival (16.8 months vs 5.6 months).[4] This translated into improved overall survival in a later analysis.

After a median follow-up of 25.2 months, the 24-month overall survival rate was 66.3% with durvalumab and 55.6% with placebo. The median time to metastasis or death was 28.3 months with durvalumab and 16.2 months with placebo. The degree of PD-L1 expression did not appear to influence the outcome significantly. Patients under 65 years old had a greater reduction in the risk of death than older patients.[5] Reflecting the trial population, the Australian approval for this indication specifies that the cancer must not have progressed following platinum-based chemoradiotherapy.

Immune checkpoint inhibitors, such as durvalumab, can cause a wide range of immune-mediated adverse reactions. These include colitis, endocrinopathies, hepatitis, nephritis, pneumonitis and rashes.[1] Depending on the severity of these reactions, treatment may have to be postponed or stopped.

Common adverse effects in the treatment of urothelial cancer and non-small cell lung cancer include fatigue, decreased appetite, diarrhoea, fever and nausea. In the phase III trial 15.4% of the durvalumab group discontinued therapy because of adverse events compared with 9.8% of the placebo group.[5]

Durvalumab adds to the range of immune checkpoint inhibitors available to treat non-small cell lung cancer. It has also been approved for urothelial carcinoma, but the results of the single-arm study[3] need to be confirmed. Like other members of the class, durvalumab is being studied in other cancers and in combination with other drugs such as tremelimumab. Whether any durvalumab regimen has an advantage over other immune checkpoint inhibitors in particular patients remains to be seen.

T manufacturer provided the product information

REFERENCES

1. Ardolino L, Joshua A. Experimental and clinical pharmacology: Immune checkpoint inhibitors in malignancy. Aust Prescr 2019;42:62-7. https://doi.org/10.18773/austprescr.2019.012
2. Massard C, Gordon MS, Sharma S, Rafii S, Wainberg ZA, Luke J, et al. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. J Clin Oncol 2016;34:3119-25. https://doi.org/10.1200/JCO.2016.67.9761

NEW DRUGS

3. Powles T, O'Donnell PH, Massard C, Arkenau HT, Friedlander TW, Hoimes CJ, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. JAMA Oncol 2017;3:e172411. https://doi.org/10.1001/jamaoncol.2017.2411
4. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017;377:1919-29. https://doi.org/10.1056/NEJMoa1709937
5. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018;379:2342-50. https://doi.org/10.1056/NEJMoa1809697

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.

Guselkumab

Aust Prescr 2019;42:105–6
https://doi.org/10.18773/austprescr.2019.031
First published 24 April 2019

Approved indication: plaque psoriasis

Tremfya (Janssen-Cilag)
prefilled syringe containing 100 mg/mL solution
Australian Medicines Handbook section 8.2.1, Immunosuppressants

Interleukins are signalling molecules involved in the regulation of the immune system. Changes in interleukins can upset this regulation and cause immune-mediated diseases. Increases in interleukins 17 and 23 can lead to the abnormal proliferation of keratinocytes seen in psoriatic skin. These interleukins have therefore become the targets for treatment when systemic therapy is needed for moderate to severe psoriasis. Interleukin 17 is a target for the monoclonal antibodies ixekizumab and secukinumab, while interleukin 23 is the target of tildrakizumab and ustekinumab.

Guselkumab is another monoclonal antibody. It binds to a subunit of interleukin 23. This prevents the interleukin from binding to its receptor so cell proliferation should be reduced.

The antibody has to be given by subcutaneous injection. A maximum concentration is reached 5.5 days later and with the recommended regimen a steady state is reached at 20 weeks. The antibody is probably catabolised and has a half-life of about 18 days.

The main efficacy studies of guselkumab included two double-blind, placebo-controlled phase III trials in patients with moderate to severe psoriasis (Table).[1,2] Guselkumab 100 mg was injected at weeks 0, 4 and then every 8 weeks. Adalimumab, a tumour necrosis factor inhibitor, was given as an active comparator. The primary outcomes were improvements in the Investigator Global Assessment and the Psoriasis Area and Severity Index (PASI). Although the trials lasted for 48 weeks, the primary end points were assessed at 16 weeks.

In the first trial (VOYAGE 1) 329 patients were randomised to receive guselkumab, 334 adalimumab and 174 placebo. After 16 weeks of treatment with guselkumab the psoriasis had cleared or was minimal in 85.1% of the patients and 73.3% had achieved at least a 90% reduction in the PASI score (PASI 90). The corresponding figures were significantly lower for adalimumab (65.9% and 49.7%) and placebo (6.9% and 2.9%). Patients in the placebo group were then switched to guselkumab and by 48 weeks they had achieved similar responses to those seen in patients who took guselkumab for the whole trial. The advantage over adalimumab was also maintained at 48 weeks.[1]

The second trial (VOYAGE 2) had a similar design with 496 patients randomised to guselkumab, 248 to adalimumab and 248 to placebo, switching to guselkumab after 16 weeks. In addition, at 28 weeks patients who responded to guselkumab were re-randomised to continue it or switch to placebo. Those switched to placebo could be re-treated if the psoriasis relapsed. After 16 weeks the psoriasis was minimal or had cleared in 84.1% of the guselkumab group, 67.7% of the adalimumab group and 8.5% of the placebo group. The respective results for PASI 90 were 70%, 46.8% and 2.4%. These responses were sustained in patients who continued taking guselkumab throughout the trial. For those switched to placebo it took about 15 weeks for the benefit

Table **Sixteen-week efficacy of guselkumab in moderate to severe plaque psoriasis**

Trial	Treatment*	Number of patients	Proportion of patients achieving primary end points	
			Minimal or cleared psoriasis %	PASI 90 %
VOYAGE 1[1]	guselkumab	329	85.1	73.3
	adalimumab	334	65.9	49.7
	placebo	174	6.9	2.9
VOYAGE 2[2]	guselkumab	496	84.1	70
	adalimumab	248	67.7	46.8
	placebo	248	8.5	2.4

* Regimens given by subcutaneous injection:
- guselkumab 100 mg at weeks 0 and 4 then every 8 weeks
- adalimumab 80 mg at week 0, 40 mg at week 1 then every 2 weeks

PASI 90 Improvement of at least 90% in the Psoriasis Area and Severity Index

NEW DRUGS

(PASI 90) to be lost. At 48 weeks 36.8% of these patients still had a PASI 90 response compared with 88.6% of those who continued treatment with guselkumab.[2]

In VOYAGE 2, 112 patients who did not respond to adalimumab were switched to guselkumab at week 28. By week 48, 66% of these patients had achieved a PASI 90 response.[2]

Another trial (NAVIGATE) looked at patients who did not respond to ustekinumab. After 16 weeks of treatment with ustekinumab 133 patients with an inadequate response were randomised to continue ustekinumab while 135 switched to guselkumab. The end point of the trial was the number of visits at which the investigators assessed the psoriasis as cleared or minimal. Between 28 and 40 weeks this outcome had been achieved at a mean of 1.5 visits with guselkumab and 0.7 visits with ustekinumab. The proportions of patients with minimal or cleared psoriasis at week 52 were 36.3% with guselkumab and 17.3% with continued ustekinumab.[3]

Infections were the most frequent adverse events in the clinical trials.[1-3] These were mainly upper respiratory tract infections. Injection-site reactions were also common. Some patients develop antibodies to guselkumab and serious hypersensitivity reactions have occurred. In view of the risk of reactivation, patients should be screened for tuberculosis before starting guselkumab. Live vaccines should not be used during treatment or for 12 weeks afterwards. Guselkumab has not been studied in human pregnancy or lactation. Whether guselkumab significantly increases the risk of malignancy is uncertain.

Biological therapies can be considered when a patient with moderate to severe plaque psoriasis requires systemic therapy or phototherapy. The trials show that guselkumab has greater efficacy than placebo and adalimumab.[1,2] It can also be considered for patients who do not respond to ustekinumab.[3] As the effects of guselkumab wear off after the drug is stopped, treatment may need to be continued for a longer duration than in the trials. This will require additional monitoring of its safety.

T manufacturer provided the AusPAR and the product information

REFERENCES

1. Blauvelt A, Papp KA, Griffiths CE, Randazzo B, Wasfi Y, Shen YK, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol 2017;76:405-17. https://doi.org/10.1016/j.jaad.2016.11.041
2. Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol 2017;76:418-31. https://doi.org/10.1016/j.jaad.2016.11.042
3. Langley RG, Tsai TF, Flavin S, Song M, Randazzo B, Wasfi Y, et al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: results of the randomized, double-blind, phase III NAVIGATE trial. Br J Dermatol 2018;178:114-23. https://doi.org/10.1111/bjd.15750

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.

Letermovir

Aust Prescr 2019;42:107
https://doi.org/10.18773/austprescr.2019.032
First published 24 April 2019

Approved indication: cytomegalovirus prophylaxis

Prevymis (Merck Sharp and Dohme)
240 mg film-coated tablets
Australian Medicines Handbook section 5.3, Antivirals

Cytomegalovirus can cause opportunistic infections in patients who are immunocompromised. For example, after haematopoietic stem cell transplantation cytomegalovirus infection can lead to pneumonia or encephalitis. As the consequences of infection can be fatal, prophylaxis has been considered, however antiviral drugs such as ganciclovir can be toxic in these patients. Some specialist centres give pre-emptive treatment if there is laboratory evidence of infection even if there are no symptoms.

Letermovir is an inhibitor of cytomegalovirus terminase. This inhibition interferes with the maturation of viral DNA.

The bioavailability of the letermovir tablets in patients who have had a stem cell transplant is influenced by ciclosporin. Lower doses are used in patients taking ciclosporin as the bioavailability is 85% compared with 35% in those taking letermovir alone. This is because ciclosporin is an inhibitor of organic ion transporters. Although little of the letermovir molecule is metabolised, it can inhibit cytochrome P450 3A. This creates the potential for interactions with drugs such as midazolam. Although not all drugs have been studied, other commonly used medicines that may interact with letermovir include statins, proton pump inhibitors, phenytoin and warfarin. Co-administration with ergot alkaloids, pimozide, and ciclosporin with simvastatin is contraindicated.

Most of the dose of letermovir is excreted in the faeces. It should not be used in severe hepatic impairment, or moderate impairment if the patient also has moderate or severe renal impairment.

The main trial of letermovir prophylaxis studied patients having allogeneic haematopoietic cell transplantation who were seropositive for cytomegalovirus but had no detectable viral DNA. Oral or intravenous letermovir was given to 373 patients and 192 were given placebo. Prophylaxis began up to 28 days after the transplant. It continued up to 14 weeks after the transplant. A daily dose of letermovir 480 mg was used, apart from patients taking ciclosporin who used 240 mg daily.

By 24 weeks after transplantation 60.6% of the placebo group had developed a clinically significant cytomegalovirus infection. In the letermovir group 37.5% developed an infection. Pre-emptive therapy was started in 16% of the letermovir group and 40% of the placebo group. All-cause mortality was 10.2% with letermovir and 15.9% with placebo.[1]

Treatment was discontinued before 24 weeks by 1.8% of the letermovir group and 0.6% of the placebo group because of adverse events. The frequency of adverse events was similar for letermovir and placebo. Cardiac adverse events, such as tachycardia and atrial fibrillation, were more frequent with letermovir than placebo (13% vs 6%). Peripheral oedema was also more frequent (14.5% vs 9.4%).[1]

The optimum use of letermovir requires more investigation. It is indicated for up to 100 days of prophylaxis, but after that time the infection rate rises. By 48 weeks the difference in all-cause mortality between letermovir and placebo was no longer statistically significant (20.9% vs 25.5%). The virus can also develop resistance to letermovir.[1]

T manufacturer provided the product information

REFERENCE

1. Marty FM, Ljungman P, Chemaly RF, Maertens J, Dadwal SS, Duarte RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. N Engl J Med 2017;377:2433-44. https://doi.org/10.1056/NEJMoa1706640

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.

NEW DRUGS

Aust Prescr 2019;42:108–9
https://doi.org/10.18773/austprescr.2019.033
First published 24 April 2019

Sofosbuvir/velpatasvir/voxilaprevir

Approved indication: hepatitis C

Vosevi (Gilead)
film-coated tablets containing 400 mg/100 mg/100 mg
Australian Medicines Handbook section 5.5, Antivirals for hepatitis C

Voxilaprevir is a new chemical entity recently approved in a fixed-dose combination with sofosbuvir[1,2] and velpatasvir.[3] Like glecaprevir and grazoprevir, voxilaprevir inhibits the NS3/4A protease involved in viral replication. Sofosbuvir is an NS5B nucleotide polymerase inhibitor and velpatasvir is an NS5A inhibitor.

The approval of this combination is primarily based on two 12-week studies in people who had previously failed treatment with direct-acting antiviral drugs (POLARIS-1 and -4).[4] The primary measure of efficacy in the trials was the proportion of patients who achieved a sustained virologic response, defined as undetectable viral RNA in a blood test 12 weeks after the end of treatment (SVR12).

Results of the POLARIS trials are summarised in the Table. Overall, sustained virologic response rates to once-daily sofosbuvir/velpatasvir/voxilaprevir were high in treatment-experienced patients.[4]

The most common adverse effects with 12 weeks of treatment were headache (26%), fatigue (22%), diarrhoea (17%) and nausea (17%). As with other direct-acting antivirals for hepatitis C, this combination comes with a warning about the risk of hepatitis B reactivation.

There are many potential drug interactions with this fixed-dose combination so checking the product information before prescribing is advisable. Its efficacy can be reduced by inducers of P-glycoprotein such as rifampicin, which is contraindicated with this product. Sofosbuvir has a potentially fatal interaction with amiodarone and concomitant use is not recommended. Other significant interactions include:

- anticonvulsants such as carbamazepine and phenytoin
- antiretrovirals such as atazanavir, lopinavir and efavirenz
- statins, particularly rosuvastatin, which is contraindicated
- St John's wort.

The solubility of velpatasvir decreases as gastric pH increases so antacids should be administered separately by four hours. Caution is urged with high doses of H_2 receptor antagonists and proton pump inhibitors.

There are no clinical studies of this combination in pregnancy. However, in animal studies, there did not appear to be any fetal adverse effects. All three drugs were found in the breast milk of lactating rats but there were no apparent adverse effects in the pups.

Following oral administration, peak plasma concentrations are reached after 2–4 hours. Dose adjustments are not required in mild–moderate renal impairment. There are no safety data in people with severe impairment or end-stage renal disease. Dose adjustments are not needed in mild hepatic impairment, but this combination is not recommended in moderate–severe hepatic impairment.

This fixed-dose combination eradicated hepatitis C infections in treatment-experienced people including those with decompensated liver cirrhosis. It was also effective in treatment-naïve patients as an eight-week treatment course (see Table).[5]

In Australia, the combination tablets are specifically indicated for treatment-experienced patients infected with:

- genotype 1, 2, 3, 4, 5 or 6 after failed previous treatment with an NS5A inhibitor such as daclatasvir, elbasvir, ledipasvir, ombitasvir or velpatasvir
- genotype 1a or 3 after failed previous treatment with a regimen containing sofosbuvir without an NS5A inhibitor. This includes those who have received sofosbuvir with or without peginterferon, ribavirin or an NS3/4A protease inhibitor such as boceprevir, simeprevir of telaprevir.

T manufacturer provided the product information

REFERENCES

1. Sofosbuvir for hepatitis C. Aust Prescr 2014;37:172-9. https://doi.org/10.18773/austprescr.2014.073
2. Ledipasvir with sofosbuvir for hepatitis C. Aust Prescr 2015;38:219-21. https://doi.org/10.18773/austprescr.2015.078
3. Sofosbuvir with velpatasvir for hepatitis C. Aust Prescr 2017;40:200-1. https://doi.org/10.18773/austprescr.2017.063
4. Bourlière M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, et al. Sofosbuvir, velpatasvir and voxilaprevir for previously treated HCV infection. N Engl J Med 2017;376:2134-46. https://doi.org/10.1056/NEJMoa1613512
5. Jacobson IM, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG, et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. Gastroenterology 2017;153:113–22. https://doi.org/10.1053/j.gastro.2017.03.047

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.

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

Patient characteristics	Treatment	SVR12
POLARIS-1 trial[4] – Treatment-experienced		
Previously taken DAA regimen containing an NS5A inhibitor Infected with genotypes 1–6, with or without cirrhosis	sofosbuvir/velpatasvir/voxilaprevir for 12 weeks (263 patients)	96% overall 93% in those with cirrhosis
	placebo for 12 weeks (152 patients, mostly genotype 1)	0%
POLARIS-4 trial[4] – Treatment-experienced		
Previously taken DAA regimen not containing an NS5A inhibitor Infected with genotypes 1–4, with or without cirrhosis	sofosbuvir/velpatasvir/voxilaprevir for 12 weeks (182 patients)	98% overall 98% in those with cirrhosis
	sofosbuvir/velpatasvir for 12 weeks (151 patients, genotype 1–3)	90% overall 86% in those with cirrhosis
POLARIS-2 trial[5] – Treatment-naïve		
Infected with genotypes 1–6, with or without cirrhosis except patients with genotype 3 and cirrhosis who were excluded	sofosbuvir/velpatasvir/voxilaprevir for 8 weeks (501 patients)	95% overall 92% in those with genotype 1a 91% in those with cirrhosis
	sofosbuvir/velpatasvir for 12 weeks (440 patients)	98% overall 99% in those with genotype 1a 99% in those with cirrhosis
POLARIS-3 trial[5] – Treatment-naïve		
Infected with genotype 3 and with cirrhosis	sofosbuvir/velpatasvir/voxilaprevir for 8 weeks (110 patients)	96% overall
	sofosbuvir/velpatasvir for 12 weeks (109 patients)	96% overall

DAA direct-acting antiviral
SVR12 sustained virologic response 12 weeks after the end of treatment, defined as undetectable viral RNA in a blood test

NEW DRUGS

Aust Prescr 2019;42:110–11
https://doi.org/10.18773/austprescr.2019.034
First published 24 April 2019

Tafenoquine succinate

Approved indication: malaria prevention

Kodatef (Biocelect)
100 mg tablets
Australian Medicines Handbook section 5.7, Antiprotozoals

Tafenoquine, a primaquine analogue, is indicated for prophylaxis against malaria in adults. It is a long-acting 8-aminoquinoline that is active at all stages of the malaria life cycle, including the liver stage where the parasites can lie dormant (as hepatic hypnozoites) before entering the bloodstream. This usually occurs less than a month after the initial infection but relapse can be delayed by several years.

It is not clear how tafenoquine kills the parasite but it has been shown to be effective in preventing infection with *Plasmodium falciparum* and *P. vivax* in people living in malaria-endemic regions.[1-4] Its approval in Australia is based on a comparative trial with mefloquine in healthy non-immune Australian soldiers (n=654) deployed to Timor-Leste.[5]

Soldiers were randomised 3:1 to tafenoquine 200 mg or mefloquine 250 mg. After a loading phase of a single dose per day for three days, soldiers entered the prophylactic phase in which they received a dose once a week for 26 weeks (± 4 weeks). On returning to Australia, soldiers entered the relapse follow-up phase where those in the mefloquine group received primaquine (15 mg twice a day) for 14 days while those in the tafenoquine group received a corresponding placebo. There were no malarial infections during the prophylactic phase with either treatment. However, during the relapse follow-up phase, there were four cases of *P. vivax* in the tafenoquine/placebo arm (4/462, 0.9%) and one case in the mefloquine/primaquine arm (1/153, 0.7%).[5] These occurred 16–20 weeks after returning from Timor-Leste.

In a safety cohort of 825 people, there were 23 serious adverse events that were thought to be related to tafenoquine treatment. These included eye disorders (7 cases), decreased glomerular filtration rate (5 cases), infection (4 cases) and gastrointestinal disorders (4 cases). The most common adverse events that led to discontinuation were increased liver enzymes, decreased haemoglobin and decreased glomerular filtration rate.

In an ophthalmic assessment of a subgroup of soldiers in the Timor-Leste study, 93.2% (69/74) had vortex keratopathy (corneal deposits) by the end of the prophylactic phase. This did not seem to affect their vision and all cases had resolved after a year.[5]

Like primaquine, tafenoquine can induce haemolytic anaemia in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency. This is especially a concern because tafenoquine has a very long half-life of 17 days. Tafenoquine is contraindicated in G6PD deficiency and in pregnancy and lactation as the G6PD status of the infant is unlikely to be known.

Although not teratogenic in animal studies, tafenoquine caused dose-related abortions in pregnant rabbits. Women of childbearing age should use contraception while taking tafenoquine and for three months after finishing prophylaxis. This drug has not been tested in children.

Tafenoquine is also contraindicated in people with current or a history of psychosis, delusions or hallucinations. Even though people with a history of psychiatric disorders were excluded from the Timor-Leste trial, sleep disturbance, depression or depressed mood and anxiety were increased. One person attempted suicide.

Following a single oral dose of tafenoquine, maximum plasma concentrations are reached after seven hours. The drug's half-life is 17 days. Tafenoquine should not be taken for longer than six months. The treatment course should include a 3-day loading dose before travel, weekly dosing while away and a single dose on return. The gastrointestinal effects of tafenoquine may be reduced by taking tablets with food. Dose adjustment in renal and hepatic impairment has not been studied.

Tafenoquine may inhibit drug transporters in the kidney which could lead to increased concentrations of renally excreted drugs. If tafenoquine is co-administered with drugs (e.g. dapsone) that have the potential to cause haemolysis in people with normal G6DP function, they should monitor their urine for dark colour and have their haematocrit checked.

Tafenoquine seemed to be as effective as mefloquine/primaquine at preventing malaria during prolonged stays in a malaria-endemic region. However, it can cause severe haemolytic anaemia and everyone must be tested to make sure they do not have G6DP deficiency before being prescribed this drug. Tafenoquine's once-weekly dosing may be preferred by some travellers.

TT manufacturer provided additional useful information

REFERENCES

1. Hale BR, Owusu-Agyei S, Fryauff DJ, Koram KA, Adjuik M, Oduro AR, et al. A randomized, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against *Plasmodium falciparum*. Clin Infect Dis 2003;36:541-9. https://doi.org/10.1086/367542

2. Lell B, Faucher JF, Missinou MA, Borrmann S, Dangelmaier O, Horton J, et al. Malaria chemoprophylaxis with tafenoquine: a randomised study. Lancet 2000;355:2041-5. https://doi.org/10.1016/S0140-6736(00)02352-7
3. Shanks GD, Oloo AJ, Aleman GM, Ohrt C, Klotz FW, Braitman D, et al. A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against *Plasmodium falciparum* malaria. Clin Infect Dis 2001;33:1968-74. https://doi.org/10.1086/324081
4. Walsh DS, Eamsila C, Sasiprapha T, Sangkharomy S, Khaewsathien P, Supakalin P, et al. Efficacy of monthly tafenoquine for prophylaxis of *Plasmodium vivax* and multidrug-resistant *P. falciparum* malaria. J Infect Dis 2004;190:1456-63. https://doi.org/10.1086/424468
5. Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, et al. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother 2010;54:792-8. https://doi.org/10.1128/AAC.00354-09

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 Food and Drug Administration website.

NEW DRUGS

Aust Prescr 2019;42:112
https://doi.org/10.18773/austprescr.2019.035
First published 24 April 2019

Telotristat ethyl

Approved indication: carcinoid syndrome diarrhoea

Xermelo (Ipsen)
250 mg film-coated tablets

Telotristat ethyl is approved for carcinoid syndrome diarrhoea. This is a rare condition which occurs in a minority of people with neuroendocrine tumours. These tumours can produce excess amounts of serotonin which causes severe diarrhoea, flushing, bronchoconstriction and cardiac valvular fibrosis. Serotonin elevations can be tracked by measuring the urinary metabolite 5-hydroxyindoleacetic acid.

Currently, these patients are treated with a somatostatin analogue (e.g. octreotide) which binds to somatostatin receptors on tumour cells and inhibits the release of serotonin. When the somatostatin analogue does not adequately control symptoms, telotristat ethyl can be added to therapy. It works by inhibiting an enzyme required for serotonin synthesis called tryptophan hydroxylase.

Telotristat ethyl is a pro-drug. After oral administration, it is hydrolysed to the active metabolite telotristat. Its terminal half-life is around 11 hours and most of the dose is eliminated in the faeces.

The recommended daily dose of this drug is 250 mg three times daily, taken with food to increase its absorption. Telotristat is not recommended in severe renal or hepatic impairment as there are limited clinical data.

The approval of telotristat is based on a study of 135 patients with carcinoid syndrome (TELESTAR).[1] They were experiencing at least four bowel movements a day despite receiving somatostatin analogue therapy for three months or more. The participants were randomised to receive telotristat (250 or 500 mg three times a day) or placebo on top of their somatostatin analogue therapy. After 12 weeks of treatment, daily bowel movements had reduced by significantly more with telotristat (1.7 fewer with 250 mg and 2.1 fewer with 500 mg) compared to placebo (0.9 fewer). A response to treatment was defined as at least a 30% reduction in bowel movements from baseline. Based on this, 44% and 42% of people who received telotristat 250 mg and 500 mg were classified as responders versus 20% who received placebo. There were no statistically significant differences in symptoms such as flushing and abdominal pain between the groups.[1]

In a supporting placebo-controlled study with a similar design (TELECAST), telotristat was assessed in 76 patients who were having fewer than four bowel movements a day. Most of them were receiving somatostatin analogue therapy. The end point was the change in urinary hydroxyindoleacetic acid, a marker of serotonin levels. After 12 weeks, this had gone up by 98% in the placebo group and down by 33% and 77% in the telotristat 250 mg and 500 mg groups.[2]

The most common adverse effects with the recommended telotristat dose of 250 mg included nausea, abdominal pain, elevated gamma-glutamyl transferase and fatigue. Constipation also occurs with telotristat. Most of these events were more common with the 500 mg telotristat dose. In an open-label 36-week extension of the TELECAST trial, depression was also more common with telotristat 500 mg and patients should be warned of this risk.[2]

In terms of drug interactions, concomitant use of short-acting octreotide decreased exposure to telotristat and its pro-drug. If short-acting octreotide is used, it should be taken at least 30 minutes after the telotristat dose. Reduced telotristat exposure has not been observed with long-acting somatostatin analogue therapy. Telotristat may decrease concentrations of cytochrome P450 (CYP) 2B6 substrates (e.g. sertraline, valproate) and CYP3A4 substrates (e.g. atorvastatin, midazolam, valproate).

Adding telotristat to somatostatin analogue therapy for 12 weeks reduced the number of bowel movements per day in patients with carcinoid syndrome. However, treatment is associated with abdominal pain, constipation and altered liver function.

T T manufacturer provided additional useful information

REFERENCES

1. Kulke MH, Hörsch D, Caplin ME, Anthony LB, Bergsland E, Öberg K, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. J Clin Oncol 2017;35:14-23. https://doi.org/10.1200/JCO.2016.69.2780
2. Pavel M, Gross DJ, Benavent M, Perros P, Srirajaskanthan R, Warner RRP, et al. Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial. Endocr Relat Cancer 2018;25:309-22. https://doi.org/10.1530/ERC-17-0455

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.

Avanafil

Aust Prescr 2019;42:113–4
https://doi.org/10.18773/austprescr.2019.043
First published 13 May 2019

Approved indication: erectile dysfunction

Spedra (A Menarini)
50 mg, 100 mg and 200 mg tablets
Australian Medicines Handbook section 13.3, Drugs for sexual dysfunction

Avanafil is another phosphodiesterase 5 inhibitor. It will compete with sildenafil, tadalafil and vardenafil as a treatment for erectile dysfunction.

By inhibiting phosphodiesterase 5, these drugs stop the breakdown of cyclic guanosine monophosphate. This molecule is responsible for the smooth muscle relaxation in the corpus cavernosum which enables the inflow of blood that results in erection.

The tablets are rapidly absorbed. Maximum plasma concentrations are reached in 30–45 minutes and in some men, erection occurs 20 minutes after a 200 mg dose of avanafil. Absorption is delayed by food. So the tablets may take longer to work if taken after a meal.

Avanafil is mainly metabolised with most of its metabolites being excreted in the faeces. It should not be used by people with severe liver disease. The half-life is 6–17 hours. As the metabolism involves cytochrome P450 (CYP) 3A4, there is the potential for many drug interactions. Avanafil is contraindicated in patients taking strong inhibitors of CYP3A4, such as itraconazole, clarithromycin and ritonavir. The dose should be limited in patients taking moderate inhibitors, such as erythromycin, and there may be reduced clearance in people taking drugs such as fluoxetine.

Avanafil also has pharmacodynamic interactions. Nitrates, such as glyceryl trinitrate, increase concentrations of guanosine monophosphate, so their action can be potentiated by phosphodiesterase inhibitors. This can cause severe hypotension. Avanafil is therefore contraindicated in patients taking nitrates. Its vasodilatory action may also have an additive effect with alcohol and antihypertensive drugs, particularly alpha blockers.

The main clinical studies of avanafil have been the subject of a meta-analysis. In these five double-blind trials, 1379 men took avanafil and 605 took placebo. The odds ratio, compared with placebo, for successful intercourse was 2.51 with avanafil 100 mg and 2.87 with 200 mg.[1]

One of the trials in the meta-analysis involved 298 men who had a nerve-sparing radical prostatectomy. The men took avanafil 100 mg, 200 mg or a placebo 30 minutes before sexual activity. Compared with baseline, over a 12-week period only 7.3% of the placebo group were able to insert their penis into their partner's vagina. The corresponding figures for avanafil 100 mg and 200 mg were 30.9% and 38.5%.[2]

A total of 712 patients who had completed two of the efficacy studies of avanafil continued in a 52–week open-label extension study. Most of the patients asked to use avanafil 200 mg. The average treatment duration was 35 weeks with only 153 men using the drug for 52 weeks. They were required to attempt sex at least four times a month. Approximately 80% were able to penetrate their partners and for 65% intercourse was successful.[3]

In the meta-analysis the main adverse effects of avanafil were headache, flushing and nasal congestion. Compared to placebo, there was not a significant difference in the number of patients stopping treatment because of adverse effects.[1]

There are some adverse effects which have occurred with other phosphodiesterase inhibitors that are an indication for stopping avanafil. These include loss of vision or hearing. In the open-label extension study one patient developed cyanopsia.[3] All phosphodiesterase inhibitors can cause priapism.

Physical causes of erectile dysfunction include cardiovascular disease, but these patients may not be suitable for treatment with avanafil. It is contraindicated in men with hypertension (>170/100 mmHg), unstable angina and congestive heart failure.

Not all patients will respond to avanafil and in those that do the erection may not last long enough for successful intercourse. It is therefore similar to other phosphodiesterase 5 inhibitors. Although the patients in the extension study favoured the 200 mg dose to the 100 mg dose, the difference in efficacy may be limited.[3]

A meta-analysis of 82 trials involving over 47,000 patients helps to suggest the place of avanafil in therapy. Although the confidence intervals overlap, avanafil appears to have lower efficacy relative to sildenafil. However, avanafil has a lower frequency of adverse effects, depending on the dose. Avanafil 100 mg had an adverse event rate similar to that of sildenafil 50 mg, but its efficacy was less.[4]

T manufacturer provided the product information

REFERENCES

1. Corona G, Rastrelli G, Burri A, Jannini EA, Maggi M. The safety and efficacy of Avanafil, a new 2(nd) generation PDE5i: comprehensive review and meta-analysis. Expert Opin Drug Saf 2016;15:237-47. https://doi.org/10.1517/14740338.2016.1130126
2. Mulhall JP, Burnett AL, Wang R, McVary KT, Moul JW, Bowden CH, et al. A phase 3, placebo controlled study of the safety and efficacy of avanafil for the treatment of erectile dysfunction after nerve sparing radical prostatectomy. J Urol 2013;189:2229-36. https://doi.org/10.1016/j.juro.2012.11.177

NEW DRUGS

3. Belkoff LH, McCullough A, Goldstein I, Jones L, Bowden CH, DiDonato K, et al. An open-label, long-term evaluation of the safety, efficacy and tolerability of avanafil in male patients with mild to severe erectile dysfunction. Int J Clin Pract 2013;67:333-41. https://doi.org/10.1111/ijcp.12065
4. Chen L, Staubli SE, Schneider MP, Kessels AG, Ivic S, Bachmann LM, et al. Phosphodiesterase 5 inhibitors for the treatment of erectile dysfunction: a trade-off network meta-analysis. Eur Urol 2015;68:674-80. https://doi.org/10.1016/j.eururo.2015.03.031

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

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

Corrections

Ertugliflozin for type 2 diabetes [Correction]

Aust Prescr 2019;42:115
https://doi.org/10.18773/austprescr.2019.036
First published 26 April 2019

The new drug commentary on ertugliflozin (Aust Prescr 2019;42:70-2) has been corrected.

The paragraph on lower limb amputations cited incorrect figures. The original text "Lower limb amputations were more common in people receiving ertugliflozin (0.47% with 5 mg dose, 0.26% with 15 mg dose) than those who did not receive it (0.07%). This has previously been found with canagliflozin which is no longer registered for use in Australia." has been replaced with "Lower limb amputations were more common in people receiving the higher ertugliflozin dose (0.47% with 15 mg dose) than those who received the lower dose (0.06% with 5 mg dose) or the comparator (0.07%). Lower limb amputations have previously been found with canagliflozin which is no longer registered for use in Australia."

Influenza: overview on prevention and therapy [Correction]

Aust Prescr 2019;42:115
https://doi.org/10.18773/austprescr.2019.045

The article on Influenza (Aust Prescr 2019;42:51-5) has been corrected.

The paragraph on National Immunisation Program funding for people at increased risk of influenza morbidity and mortality should have included 'Aboriginal and Torres Strait Islanders aged over six months and over' (rather than just 'Aboriginal and Torres Strait Islander children aged six months to five years' and 'Aboriginal and Torres Strait Islanders aged over 15 years').

A:

ANSWERS TO SELF-TEST QUESTIONS

1 True
2 False
3 False
4 False

EDITORIAL OFFICE

For general correspondence such as Letters to the Editor, contact the Editor.

Postal The Editor
Australian Prescriber
Level 5, 15 Moore Street
Canberra, ACT 2600

Telephone +61 2 8217 8700

Email info@australianprescriber.com

Website nps.org.au/australian-prescriber

Twitter @AustPrescriber

SUBSCRIPTIONS

Australian Prescriber is published every two months online. All content is accessible free of charge in full text at nps.org.au/australian-prescriber. New drugs are published between issues as they become available.

An email alert can be sent to you when *Australian Prescriber* publishes new material. Subscribe or update your details at nps.org.au/australian-prescriber

For back issues, and copies of the Anaphylaxis wallchart and Switching-antidepressants poster, email info@australianprescriber.com

Australian Prescriber

AUSTRALIAN PRESCRIBER IS INDEXED AND ARCHIVED BY

- Academic Search Complete
- Academic Search Research and Development
- Australian Public Affairs Information Service - Health
- EMBASE/Excerpta Medica
- Emerging Sources Citation Index
- PubMed Central

Typesetting by Stripe Design, Canberra
ISSN 1839-3942

Published by NPS MEDICINEWISE

Independent. Not-for-profit. Evidence-based. NPS MedicineWise enables better decisions about medicines, medical tests and other health technologies. We receive funding from the Australian Government Department of Health.