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Issues abound before, during and after prescribing a new drug — whether the drug is new to you, your patient or both. Evaluating the suitability of the new drug for your patient includes assessing its efficacy and safety profile. When adding a new drug, it can be challenging to communicate the uncertainties and limitations of the available evidence with your patient. Inside this *NPS News* you will find practical examples of how to assess efficacy and safety against promotional claims, as well as ways to consider affordability and patient acceptance.

New is in the eye of the beholder

Is a new drug always that new? Perhaps it is a member of an existing class (do we really need eight ACE inhibitors?) or a new formulation (such as fentanyl transdermal patches). Only a limited number of the drugs developed each year add significantly to available therapies.

Maybe the drug is new to the Australian market but has been used overseas. Such clinical experience and post-marketing surveillance are valuable when assessing the drug's benefits and harms in the Australian context.

Remember, a drug well known to you can still be new to your patient. Consider an elderly patient with uncontrolled hypertension taking hydrochlorothiazide; you might introduce a second antihypertensive agent, or a combination product, and either of these options will be new to your patient.

Finally, a patient with impaired glucose tolerance whose efforts to quit smoking, lose weight (by improving diet with regular exercise) and reduce alcohol consumption¹ have delayed, but not prevented, the development of type 2 diabetes. Such a patient requires a 'new' drug, which may be quite well known to you.

Pressure to prescribe a new drug

Patient expectations and catchy promotional claims may contribute to pressure to prescribe a new drug. Perhaps your patient has requested a specific drug after hearing about it from a friend. It may be that a recent pharmaceutical company representative's visit provided information that appears compelling.

Why a new drug?

Before prescribing, evaluate why the new drug might be introduced. Is the new drug:

- treating a newly diagnosed condition?
- replacing existing therapy?
- adding to existing therapy?

How?

How to 'unwrap' a new drug

Efficacy and safety are key to assessing a new drug's possible place in therapy (see inside for examples).

Once efficacy and safety have been established, consider affordability and patient acceptance (see inside for examples).



NPS is an independent, non-profit organisation for Quality Use of Medicines, funded by the Australian Government Department of Health and Ageing.

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How to 'unwrap' a new drug

Has the new drug been shown to be more effective than existing therapy?

Example: Alendronate 70 mg + vitamin D₃ (cholecalciferol) 2800 units (Fosamax Plus)

Bisphosphonates (such as alendronate and risedronate) are considered first-line therapy for treating patients with osteoporosis and a minimal-trauma fracture.^{2,3} Whether a vitamin D₃ supplement is needed in addition to alendronate depends on the person's vitamin D₃ status and the risk of deficiency.^{2,3} People without vitamin D₃ deficiency or obvious risk factors are unlikely to benefit from vitamin D₃ supplementation.

Questions to consider when evaluating promotional claims about efficacy



Did the trial compare the new drug with the current first-choice drug at effective doses?

Alendronate with vitamin D₃ was compared with alendronate alone in the (as yet) unpublished efficacy trial.⁴

Was the trial randomised and double-blind?

Yes.

Did the trial reflect the population in which the drug will be used?

Participants:

- agreed to limit sunlight exposure for the 15-week trial
- were excluded if their serum hydroxyvitamin D (25-OHD) concentration was < 22.5 nmol/L.

Serum hydroxyvitamin D deficiency and insufficiency^{2,5,6}

Severity of deficiency	Serum 25-OHD range (nmol/L)
Mild	25–50
Moderate	12.5–25
Severe	< 12.5

About 2 in every 10 study patients had a serum 25-OHD concentration < 37.5 nmol/L at baseline, which:

- decreased to about 1 in 10 patients taking alendronate + vitamin D₃
- increased to about 3 in 10 patients taking alendronate alone after 15 weeks of treatment.



These results may apply to people who undergo an unavoidable change in their sunlight exposure, such as someone having a fall requiring hospitalisation. They do not apply to people with normal or mildly insufficient serum 25-OHD concentration (25–50 nmol/L) who have adequate sunlight exposure, or who have long-term underexposure to sunlight and so may already be vitamin D deficient and therefore need higher doses.

Did the trial measure long-term effects on patient-relevant outcomes rather than relying on surrogate markers?

This 15-week trial was too short to measure any long-term effects such as fracture rates. It focused on serum 25-OHD concentrations as a surrogate marker.

Is the advantage likely to be clinically significant?

Recent consensus guidelines state that vitamin D 400 units/day is probably enough to prevent deficiency in people who cannot obtain adequate sunlight.^{5,6} However, people with a low vitamin D₃ level due to diet and lack of sunlight may already be deficient, and a high-dose supplement would be indicated.^{2,6}

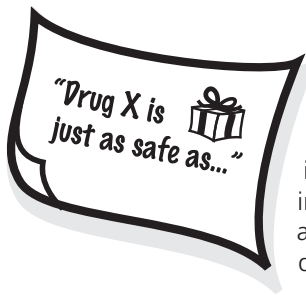


Therefore, the vitamin D₃ content of Fosamax Plus is:

- inadequate to address vitamin D₃ deficiency
- inadequate for preventing deficiency in high-risk groups.

The vitamin D₃ content of Fosamax Plus can prevent deficiency in people aged 51–70 years who are not vitamin D₃ deficient but who do not get enough sunlight. However, it has not been shown to increase the efficacy of alendronate in preventing fractures.

There is no need to switch patients with vitamin D₃ deficiency, or at risk of becoming vitamin D₃ deficient, from alendronate to the combination. Furthermore, the benefits of vitamin D₃ supplementation in people with adequate serum vitamin D₃ concentrations are unproven.⁵



Has the new drug been shown to be safe?

At the time of marketing a new drug it is unlikely that the full safety profile is understood. Most clinical trials focus on efficacy rather than safety, and the number of patients in the trials is often limited to a few thousand. Thus not all potential adverse effects are known and their true incidence may only become apparent after the drug is more widely used. It is important to report adverse reactions to new drugs, as surveillance of these effects can add to our knowledge of the drug (see Reporting below).

Questions to consider when evaluating promotional claims about safety

Example: Pimecrolimus cream (Elidel)

Pimecrolimus cream has been available in Australia since 2003 and is PBS-subsidised for use as second-line therapy for facial atopic dermatitis in adults and children aged 3 months and older when topical corticosteroids are either contraindicated or have failed to control the dermatitis.

What are the incidence and severity of side effects?

About 20% of patients experience irritation at the site of application.⁷ In trials (with around 2000 patients in total) these itching or burning sensations, mostly mild to moderate in severity, started within 1–5 days of treatment and lasted no more than 5 days.⁸ Application-site reactions, including burning, irritation and itching, were more common with pimecrolimus than with topical corticosteroid creams in one randomised controlled trial.⁹ Local irritation may be discouraging for children, as they have poor tolerance of preparations that sting.¹⁰

Are long-term safety data available?

Pimecrolimus is an immunosuppressant. Clinical trials of topical pimecrolimus of up to 2 years have not shown an increased incidence of malignancy. However, a number of cases of malignancies, including lymphoma and skin cancers, have been reported worldwide in people who had used pimecrolimus¹¹, although whether pimecrolimus was the cause has not been established.

In early 2006, warnings relating to malignancies were added to the approved product information for pimecrolimus in Australia, Europe and the USA.^{8,11}

This is important because the long-term effects of exposure to topical immunosuppressants are not known, a concern particularly relevant in children.

Which patients are most at risk of adverse effects? What strategies may minimise risk?

As a precaution, exposure to pimecrolimus should be minimised by applying it to the smallest practicable area for the shortest possible time.

Pimecrolimus cream should not be used continuously; treat each episode of atopic dermatitis with pimecrolimus for a maximum of 6 weeks (3 weeks for infants). It should not be applied to areas affected by pre-malignant changes (e.g. actinic keratoses) or where skin cancers have been removed. Patients are advised to protect treated areas from exposure to the sun by using sunscreen and protective clothing.⁷

Which patients should not receive the drug?

Pimecrolimus should not be used in immunosuppressed people, in pregnant women or in patients receiving phototherapy.



Reporting

Reporting suspected adverse drug reactions to new drugs helps define safety

A new drug may be used in a few thousand patients before marketing, but exposure to at least 30 000 people is needed to reliably detect an adverse drug reaction (ADR) that occurs in 1 in 10 000 patients.¹² Over 200 000 adverse events have been reported to the Adverse Drug Reactions Advisory Committee (ADRAC) since 1964; 9823 of these were received in 2004.¹³

Keep an eye on the *ADRAC Bulletin*, which highlights emerging safety issues (from ADR reporting) and lists 'Drugs of Current Interest'. The *ADRAC Bulletin* is now available electronically — register for free email updates (at www.tga.gov.au/adr/adrac-bulletin-subscribe.asp).

How?

How to report suspected adverse drug reactions

Use the ADRAC *blue card* (www.tga.gov.au/adr/bluecard.htm), this is also available in *Australian Prescriber*.

Adding a new drug


Affordability and patient acceptance of a new medicine are secondary issues to consider when tailoring therapy for your patient.

Evaluating promotional claims about affordability

Does it have advantages to the patient other than cost?

Perhaps a patient's low-density lipoprotein-cholesterol concentration remains elevated despite compliance with lifestyle measures (diet and exercise) and simvastatin 80 mg daily. Ezetimibe may be added as a separate tablet (Ezetrol) or a combination tablet containing simvastatin plus ezetimibe (Vytorin).

The combination tablet is cheaper for the patient (because only one co-payment is required) and may be more convenient (because only one tablet is needed) compared with simvastatin plus ezetimibe prescribed separately.



"Drug X is affordable for more patients"

Is the drug PBS listed? What is the PBS indication?

Not all Australian-approved uses of a medicine are able to be prescribed on the PBS. Lumiracoxib 200 mg tablets are PBS listed for symptomatic treatment of osteoarthritis. Other indications registered with the Therapeutic Goods Administration — acute pain and primary dysmenorrhoea — are *not* PBS listed.¹⁴

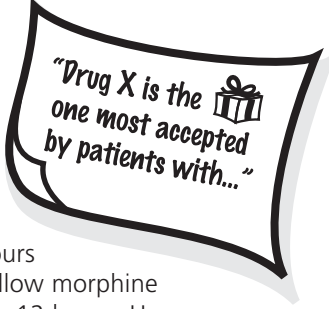
Does the drug have a brand price premium?

Two bioequivalent brands of modified-release paracetamol, Panadol Osteo and Duatrol, are on the PBS for osteoarthritis¹⁵. Panadol Osteo has a \$4.88 premium (which doubles its price for people with concession cards).

Evaluating promotional claims about acceptability and/or convenience

Consider the formulation, route of administration and dose frequency

Perhaps fentanyl transdermal patches may be useful for a patient with cancer pain who develops difficulty swallowing, and for whom fentanyl is an appropriate alternative analgesic. This patient may appreciate replacing a patch every 72 hours rather than struggling to swallow morphine sustained-release tablets every 12 hours. However, the safe use and disposal of fentanyl patches requires adequate explanation.³ The patient and/or carer may not accept this, which may make fentanyl patches an unsuitable choice.




"Drug X is the one most accepted by patients with..."

Consider any special instructions for use

For example, alendronate tablets must be taken in the morning with a full glass of water at least 30 minutes before food or drink.³ This may not be suitable for a patient unable to sit upright for extended periods, or who has dementia.

Certain devices, such as the tiotropium HandiHaler, may be difficult for a patient with limited manual dexterity or who is visually impaired.



"Drug X is more convenient for your patient to use"

Independent information

Where? Where to find it.

The National Prescribing Service Limited (www.nps.org.au) provides accurate, balanced, evidence-based information about medicines. *NPS RADAR* (Rational Assessment of New Drugs and Research) provides updates on new drugs as they are listed on the PBS.^{4,11} Register (www.npsradar.org.au) for free email updates.

Australian Prescriber (www.australianprescriber.com) considers the merits of drugs recently made available in Australia.

Telephone the *NPS Therapeutic Advice and Information Service* (TAIS) 1300 138 677 (local call cost except for mobile phones) for evidence-based information about medicines.

Australian Medicines Handbook (www.amh.net.au) provides concise practical comparative drug information.

Therapeutic Guidelines (www.tg.com.au) produce guidelines for therapy from the latest world literature, interpreted and distilled by Australian experts.

The Cochrane Collaboration (www.cochrane.org) provides information about the effects of health care.

Effective communication is crucial when adding a new drug

Effective communication increases patient satisfaction and involvement in decision making — resulting in realistic expectations of outcomes.^{16,17}

Patients have access to information of variable quality through the media and Internet; their expectations of what their health professional can provide may be influenced by this. Effective communication between patients and health professionals is vital.¹⁸ An American study showed that primary care physicians fulfilled 3 of 5 expected elements of communication on average (name and purpose of new drug; directions for, and duration of, use; and adverse effects) when prescribing a new drug.¹⁹

Knowledge of the patient's decision-making preferences and communication needs (such as literacy level) are essential for effective communication between a health professional and patient.²⁰ Views of benefits and harms vary between patients, which adds to the challenge of providing a balanced discussion about uncertainties and limitations of the evidence. Patients' understanding may increase when different forms of communication are used, for example: verbal, written, illustrative diagrams, cartoons/graphics, video, computer-based. This is especially true when information is structured, tailored and/or interactive.¹⁶

Review your patient's medicines before adding a new drug

Considering a new drug for your patient may provide an opportunity to participate in a Home Medicines Review (HMR). Medicare provides guidance for when an HMR may be appropriate, and a rebate for a GPs' involvement in an HMR (MBS Item 900).²¹

An HMR may improve patient health by identifying and resolving medication-related problems.^{22,23} Between October 2001 and April 2005, more than 70 000 HMRs were conducted across Australia; three-quarters of these were in patients aged over 65 years.²⁴

More information about the HMR program is available from the Australian Government Department of Health and Ageing (www.health.gov.au), Australian Divisions of General Practice (www.adgp.com.au/site/index.cfm?display=348) and the Pharmacy Guild of Australia (beta.guild.org.au/mmr).

What information is available for my patient?

Consumer medicine information (CMI)

CMIs are available in prescribing and dispensing software, eMIMS, the APP Guide, from pharmaceutical companies and the NPS website (www.nps.org.au/consumers then 'Consumer Medicine Information' in the right-hand panel).

Information about Medicines Line

Medicines Line provides your patient with independent information their medicines. Medicines Line (1300 888 763) is available between 9 am and 6 pm Monday to Friday, Eastern Standard Time (EST) for the cost of a local call (mobile calls may cost more).

Toolkit for effective communication

The National Health and Medical Research Council has recently developed an evidence-based toolkit to help patients and health professionals learn how to communicate effectively. The toolkit can also be downloaded (www.nhmrc.gov.au/publications/synopses/hpr25syn.htm).

What's in an HMR for my patient?

- Enhanced understanding of their medicines and how to find more information.
- Increased confidence in managing their medicines.
- Advice about appropriate storage of medicines and handling of expired or unwanted medicines.
- Optimisation of their medicine regimen.²¹

What's in an HMR for me?

- Collaboration and improved relationships with other health professionals.
- Enhanced understanding of all the medicines (prescription, over-the-counter, and complementary) and related devices currently or recently being taken/used by a patient.²¹

Erratum *NPS News 47: Analgesic options for pain relief*

In *NPS News 47* under the heading 'Thinking about tramadol' it was incorrectly stated that tramadol is contraindicated in people taking serotonergic drugs.

Tramadol is contraindicated in combination with MAOIs and moclobemide. It may be used **with caution** in combination with

other serotonergic drugs (such as SSRIs, mirtazapine, venlafaxine and St John's wort), although these combinations should be avoided if possible because of the risk of serotonin syndrome.

All versions of *NPS News 47* on the NPS website have been corrected. We apologise for any confusion.

Other information resources

Where to find Information provided by Australian government departments

- The clinical trials register at the National Health and Medical Research Council (www.nhmrc.gov.au).
- Pharmaceutical Benefits Advisory Committee (PBAC) outcomes and public summary documents (www.health.gov.au/internet/wcms/publishing.nsf/content/pbac-outcomes-and-public-summary-documents).
- Schedule of Pharmaceutical Benefits (PBS)
General PBS queries 132 290
PBS information Line 1800 020 613.
- Therapeutic Goods Administration (www.tga.gov.au).

Where to find Information provided by the pharmaceutical industry

- Product information.
- References supporting promotional material.
- The Medicines Australia *Code of Conduct*, which sets out voluntary standards for the ethical marketing and promotion of prescription pharmaceutical products in Australia. See www.medicinesaustralia.com.au for more information.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.



National Prescribing Service Limited

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NPSN0118