

New (and old) ways of looking at new drugs

Many drugs become part of the medical landscape in any given year: in 2002, 100 recommendations were made to the Therapeutic Goods Administration (TGA) for drug registrations or new indications and there were over 500 new and revised listings to the Pharmaceutical Benefits Scheme (PBS).

Health professionals face the daunting task of keeping up with this information. Revisiting principles to critically assess new drugs can assist health professionals in this endeavour, as can a new NPS service called RADAR.

RADAR: the Rational Assessment of Drugs and Research

In response to demand from health professionals for timely access to information about new drugs, NPS launched RADAR in November 2003. RADAR, in conjunction with *Australian Prescriber's* New Drugs section, provides independent information about new drugs as they come on to the market or are listed on the PBS; or when research is published that significantly changes the way a drug is used or prescribed in primary care.

RADAR provides information when it's needed

RADAR provides independent, evidence-based information from a quality use of medicines perspective, including:

- the place in therapy of new drugs relative to existing treatments
- important issues regarding safety or dosing
- discussion points to assist health professionals explain this information to patients.

Of particular interest to health professionals is the inclusion of the reasoning behind why a medicine has a particular PBS listing, based on documentation provided by the Pharmaceutical Benefits Advisory Committee (PBAC) that has until now been inaccessible. This is an important first step along a pathway to increase transparency of the PBS process for health professionals and consumers.

Concise commentaries on newly published research that significantly impacts on primary care therapeutic decision-making will also be featured, allowing health professionals to quickly decipher what this research means for them and their patients. The NPS commentary comparing the results of the ALLHAT and ANBP2 studies in early 2003 is an example of what can be expected in future issues of RADAR.

Information on drugs relevant to primary care

NPS has developed criteria to assess which drugs are most relevant to primary care and guide the focus of RADAR:

- there is an important quality use of medicines issue about the drug
- the drug will have an impact on prescribing by GPs and other prescribers
- the drug is considered to have a potential impact on PBS utilisation
- the PBAC (or one of its subcommittees) requests NPS to provide education around a particular PBS listing
- there is significant media coverage (trade or lay) causing therapeutic uncertainty.



Rational Assessment of Drugs and Research

Keep track of what's out there

RADAR is predominantly an online service. To have your personal copy delivered directly to your desktop free-of-charge, register at www.npsradar.org.au

Inside ▶

Weighing up the cost-effectiveness of new drugs

Deciding whether to use a new drug

What else you can do

National Medicines Symposium 2004

Weighing up the cost-effectiveness of new drugs

We all have some understanding of the term *cost-effectiveness*—for example, when buying a car, as well as price we might consider size, fuel efficiency and features such as air-conditioning or a CD player—but what does it mean in relation to health, and how do we measure it?

To be suitable for PBS listing, a drug must meet a clinical need *and* be cost-effective. New drugs may sometimes offer an improvement over existing therapies, but they are usually more expensive too. An economic evaluation is a method for quantifying the additional cost of any extra benefit. Economic evaluations therefore help to guide decision-making about the relative cost-effectiveness, or value-for-money, of different therapies.

Health economics terms explained

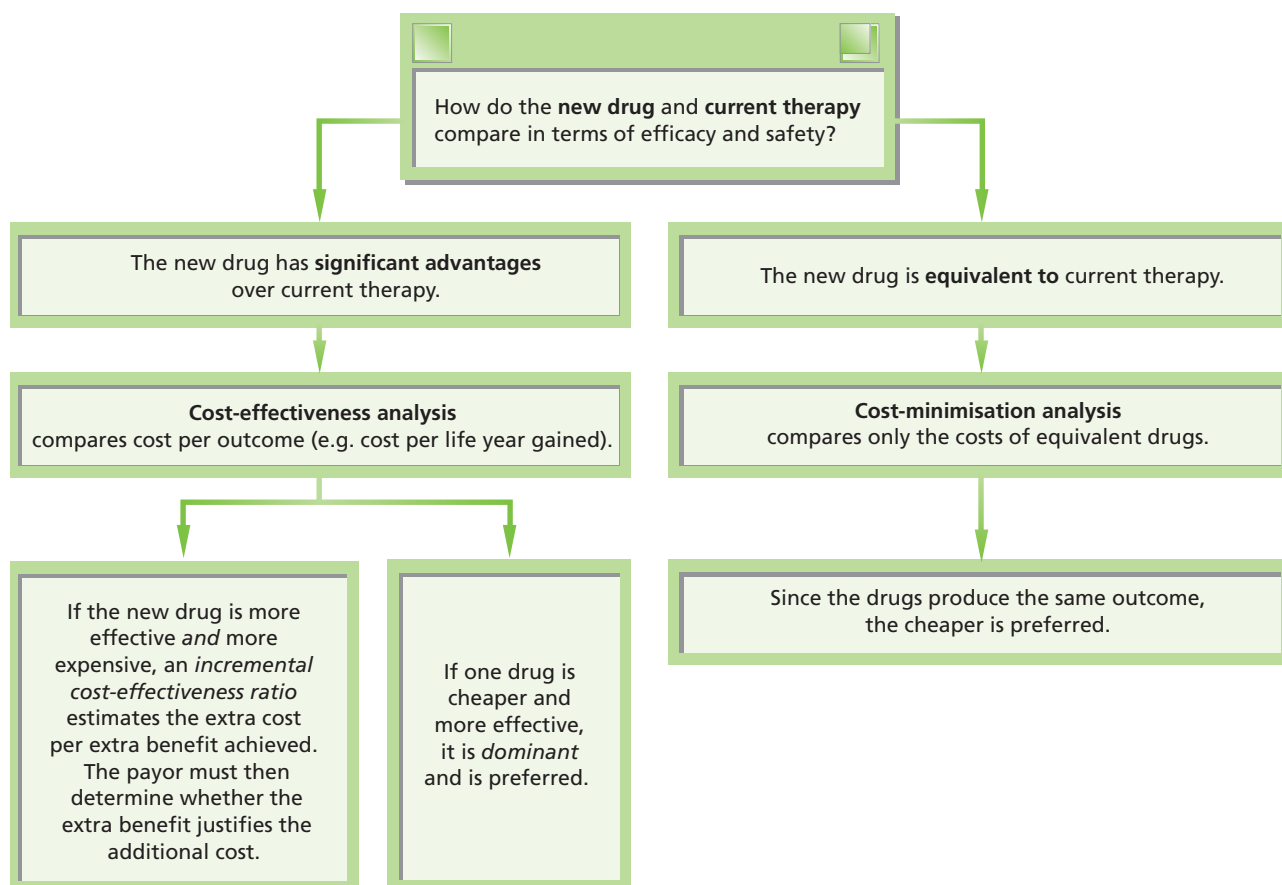
Cost-minimisation or cost-effectiveness analyses are most commonly used when evaluating drug applications for PBS listing and are described below (Figure 1).

Other health economics terms are explained in the accompanying glossary.

Economic analysis relies on sound clinical evidence

The quality of the clinical evidence base for an economic evaluation and the appropriateness of the comparator are factors in the success of an application for PBS listing. Well-designed and conducted studies are likely to give the most accurate estimate of a drug's efficacy on which to base a useful analysis. An economic evaluation must also use an appropriate comparator to demonstrate that the new drug provides as good or better value for money than current standard care.

Figure 1: Comparison of cost-effectiveness and cost-minimisation



PBS restricted benefit and authority required listings

Restricted benefit or authority required listings may be used to limit the PBS use of a drug to the population where it is cost-effective.

For example, clopidogrel is approved by the TGA for secondary prevention of vascular events and in combination with aspirin in acute coronary syndrome.¹ However, it is considerably more expensive than aspirin and has only a small efficacy advantage^{2,3} (Table 1). A PBS authority listing limits its subsidised use to people with a history of symptomatic events on aspirin or for whom aspirin is unsuitable.

Authority listings may also be designated when there are safety concerns about a drug. For example, an authority was added to the cisapride listing because of the potential for QT prolongation leading to serious cardiac arrhythmias.⁵ Cisapride is no longer subsidised for gastroesophageal reflux; its use is restricted to the treatment of gastroparesis where the diagnosis has been made or confirmed by a consultant physician.

Table 1: Cost of clopidogrel to prevent one additional cardiovascular event compared to aspirin

Clinical trial inclusion criteria	Treatment	Number-needed-to-treat with clopidogrel to prevent one additional stroke, myocardial infarction or cardiovascular death*	Drug cost of clopidogrel to prevent one additional event [†]
Ischaemic stroke, myocardial infarction or symptomatic atherosclerotic peripheral arterial disease ²	Clopidogrel compared to aspirin	115 people for 2 years	\$251 970
Acute coronary syndrome ³	Clopidogrel plus aspirin compared to aspirin alone	48 people for 9 months	\$38 899

* For example, 115 people need to be treated for 2 years with clopidogrel instead of aspirin to prevent one additional cardiovascular event.

† PBS cost of drug.

Deciding whether to use a new drug

Before prescribing a new drug, you should be convinced that it offers an advantage over current therapy.

While drug registration and PBS listing indicate the quality, safety, efficacy and cost-effectiveness of the new drug, neither process defines the new drug's appropriate use in the context of existing treatments. Using a *personal formulary* gives you a yardstick against which to measure new drugs.

A personal formulary is the selection of drugs from which you usually prescribe. Choose your personal formulary on the basis of good quality evidence, focusing on comparative efficacy, safety, cost and convenience. A series in *Australian Family Physician* discusses selecting and using a personal formulary.¹

Comparing new drugs with your personal formulary

Compare your current choice and the new drug for efficacy, safety, cost and convenience. See inside this *NPS News* for a checklist of questions to ask about new drugs.

Cont'd above right



Comparing new drugs with your personal formulary (cont'd)

Example: montelukast in paediatric asthma

A pharmaceutical company representative visits you to promote montelukast in children with asthma. You currently prescribe low-dose inhaled corticosteroids for children needing preventive therapy. You ask the representative for studies comparing montelukast and inhaled corticosteroids in children.

Efficacy

At the time of marketing, evidence for a drug's efficacy is often inadequate to establish its place in therapy. Studies conducted for registration often compare a new drug to placebo and tend to measure surrogate markers rather than long-term effects on patient-relevant clinical outcomes.

Montelukast in paediatric asthma: Efficacy

The efficacy of montelukast and inhaled corticosteroids in children has not been compared; to date, montelukast studies in children have been placebo-controlled and have used surrogate measures, such as symptom diaries or FEV₁, rather than asthma exacerbations.^{2,3}

Safety

Rare or long-term side-effects of new drugs are usually unknown since studies conducted for registration tend to be short and involve relatively small numbers of people. Those susceptible to adverse effects, such as people taking other medicines or the very elderly, are often excluded. Experience with drugs in the same class is no guarantee of safety; for example, cerivastatin was withdrawn from the market because of serious muscle side-effects, despite other members of the statin class being widely used for a number of years.

Montelukast in paediatric asthma: Safety

Montelukast appears to be well tolerated, although long-term safety data are limited. Churg–Strauss syndrome, an eosinophilic vasculitis, has occasionally been reported, but it is not known whether it is causally related to montelukast.

Inhaled corticosteroids have a more established adverse effect profile than montelukast. While there are some concerns about systemic adverse effects, particularly growth suppression in children, available evidence suggests that final adult height is unlikely to be affected.⁴

Cost

Consider cost to the patient and to the community, including costs of monitoring and treating side-effects.

Montelukast in paediatric asthma: Cost

Montelukast is PBS listed for children aged 2–14 years with frequent episodic or mild persistent asthma. A month's supply costs \$46.72.⁵

Low-dose corticosteroid metered-dose inhalers typically used in children are PBS-listed as unrestricted benefits. The cost of a month's supply is generally less than \$20.00.⁵

Convenience

Dosing frequency, route of administration and the need for monitoring affect a drug's acceptability to patients.

Montelukast in paediatric asthma: Convenience

A once-daily montelukast tablet may be more convenient than using an inhaler two or three times a day, but children will still need to learn to use inhaler devices for symptom relievers.

Montelukast in paediatric asthma

The verdict

You decide not to replace inhaled corticosteroids as your preferred drugs. Montelukast is potentially more convenient for children than inhalers but there is no evidence to suggest an efficacy or safety advantage over inhaled corticosteroids, and it costs more.

What else you can do

Report suspected adverse reactions to new drugs

A new drug may be used in a few thousand patients before marketing, but exposure of 30 000 people or more is needed to reliably detect a side-effect occurring in 1 in 10 000 patients.¹ Post-marketing surveillance is crucial for defining the safety profile of a new medicine. Suspected adverse reactions to new drugs should be reported to the Australian Drug Reactions Advisory Committee (ADRAC).

Adverse drug reactions can be reported

- using the ADRAC *blue card*, available in the PBS book and in the ADRAC bulletin, distributed with *Australian Prescriber*
- by phone to ADRAC on 1800 044 114
- on-line at the TGA's electronic reporting system: <http://www.tgasime.health.gov.au/> go to *Adverse Drug Reactions*
- to the pharmaceutical company, which is legally obliged to report all adverse events to ADRAC
- by members of the public to the Adverse Medicine Events line on 1300 134 237.

Provide consumer medicine information with samples

Pharmaceutical companies may provide samples as part of a *familiarisation program* to encourage rapid uptake of a new drug, often before its PBS listing. If you use samples, remember to provide a consumer medicine information leaflet (CMI) with them, because patients will not usually be able to obtain one from a pharmacy unless the drug has been dispensed. CMI should be provided to you when you receive samples—if not, request them from the company representative.

Be aware of the Medicines Australia Code of Conduct for drug promotion

Drugs must be promoted in line with the Medicines Australia Code of Conduct, which states that promotional claims should be accurate, balanced, correct and fully supported by the product information or published literature. New drugs must not be promoted before they are registered by the TGA. Report any concerns about drug promotion to:

Medicines Australia
Level 1/16 Napier Close
Deakin ACT 2600 (02 6282 6888)

The Code of Conduct is available at www.medicinesaustralia.com.au



National Medicines Symposium 2004

Quality Use of Medicines – time for total integration

Wednesday 28 – Friday 30 July 2004

Brisbane Convention and Exhibition Centre, Brisbane Australia

Go to <http://www.nps.org.au> > Corporate and media

Early bird registrations and abstracts close on 24 March 2004

For more information contact Elana Huthnance at NPS by phone on 02 8217 8700 or email at ehuthnance@nps.org.au



National Prescribing Service Limited



Contributing reviewer:

Dr Suzanne Hill
Senior Lecturer in Clinical Pharmacology
School of Medical Practice and Population Health
Faculty of Health
Newcastle University

Reviewers

Dr James Best, General Practitioner

A/Prof Nick Buckley, Clinical Pharmacologist, The Canberra Hospital

Ms Jan Donovan, Consumer

Dr John Dowden, Australian Prescriber

Ms Simone Rossi,
Australian Medicines Handbook

Prof John Murtagh, Dept of General Practice, Monash University,
Melbourne

Ms Susan Parker,
Australian Self-Medication Industry

Any correspondence regarding content should be directed to the
NPS. Declarations of interest have been sought from all reviewers.

References:

Weighing up the cost-effectiveness of new drugs

1. Sanofi-Synthelabo Australia Pty Ltd. Plavix (clopidogrel) Product Information. MIMS Online Version 1.1. 1 August–31 October, 2003.
2. CAPRIE Steering Committee. Lancet 1996;348:1329–39.
3. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. N Engl J Med 2001;345:494–502.
4. Commonwealth Department of Health and Ageing. Schedule of Pharmaceutical Benefits. 1 August 2003.
5. MacDonell D. Aust Prescr 2000;23;93–7.

Deciding whether to use a new drug

1. Shakib S, George A. Aust Fam Physician 2003;32:35–8, 147–9, 243–6, 325–8, 438–41, 504–7, 621–4, 702–4. <http://www.racgp.org.au/folder.asp?id=785> (accessed 16 October 2003).
2. Knorr B, et al. Pediatrics 2001;108(3):e48.
3. Knorr B, et al. JAMA 1998;279:1181–6.
4. van Asperen P, et al. Med J Aust 2002;176:168–73.
5. Commonwealth Department of Health and Ageing. Schedule of Pharmaceutical Benefits. 1 August 2003.

What else you can do

1. World Health Organization. The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products. 2002. http://www.who.int/medicines/library/qsm/ip_booklet.pdf (accessed 16 October 2003).

*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 individual clinical circumstances of each patient.*



National Prescribing Service Limited

Our goal To improve health outcomes for Australians through prescribing that is: ▲ safe ▲ effective ▲ cost-effective
Our programs To enable prescribers to make the best prescribing decisions for their patients, the NPS provides:
▲ information ▲ education ▲ support ▲ resources

Level 7 / 418A Elizabeth Street Surry Hills NSW 2010

Phone: 02 8217 8700 | Fax: 02 9211 7578 | email: info@nps.org.au | net: <http://www.nps.org.au>

Questions to ask when evaluating a new drug

The checklist below has been designed to help you assess new drugs in comparison to your current practice. You may like to use it as a basis for discussion when pharmaceutical company representatives visit you to promote new drugs.

What is new about the drug?

- Is it a member of an existing class or a new formulation, or is it a genuine innovation?

Is there good quality evidence that the new drug has an efficacy advantage over existing therapy?

- Do studies compare the new drug to the current drug of choice at effective doses?
- Is the advantage likely to be clinically significant?
- How strong is the evidence?
 - Are studies randomised and double-blind?
 - Do studies include enough patients for firm conclusions to be drawn?
 - Do studies reflect the population in which the drug will be used?
 - Do studies measure long-term effects on patient-relevant outcomes rather than relying on surrogate endpoints?

Has the new drug been shown to be safe?

- What are the incidence and severity of side-effects?
- Are long-term safety data available? Has the drug been used overseas?
- Which patients are at most risk of side-effects? Which patients should not receive the drug?
- In which patients is safety unknown (such as pregnant women or people with hepatic impairment)?

Is the new drug affordable for patients and value for money compared to existing therapy?

- If it is more expensive than existing therapy, does it have advantages that justify the extra cost?
- Is it PBS-listed? What is its PBS indication?
- Does it have a premium (such as a brand price premium or therapeutic group premium) over other drugs?
- Are there cheaper alternatives (e.g. other drugs in the same class)?

Is the drug likely to be convenient to use and acceptable to patients?

- How acceptable is the formulation, route of administration and dose frequency likely to be to patients?
- Are any special instructions needed to use it (such as drug–food interactions, or instructions for using a new device)?
- Is monitoring required?



National Prescribing Service Limited

Our goal To improve health outcomes for Australians through prescribing that is: ▲ safe ▲ effective ▲ cost-effective
Our programs To enable prescribers to make the best prescribing decisions for their patients, the NPS provides:
▲ information ▲ education ▲ support ▲ resources

Level 7 / 418A Elizabeth Street Surry Hills NSW 2010

Phone: 02 8217 8700 | Fax: 02 9211 7578 | email: info@nps.org.au | net: <http://www.nps.org.au>

Glossary*

Below are definitions for some commonly used evidence-based medicine terms, which you may like to refer to when reading clinical papers. Definitions for health economics terms, which will be used in NPS Radar, are also provided.

Evidence-based medicine terms

The following scenario is provided as a basis for examples in the definitions below.

In a study of stroke prevention, 100 people take a new drug and 100 people take placebo. After 1 year of treatment, 8 people in the treatment group and 10 in the control group have had a stroke.

Absolute risk

The probability that a person will experience a specified outcome during a specified period.

Example: The absolute risk of stroke in the control group is $10/100 = 0.1$, or 10%, and in the treatment group is $8/100 = 0.08$, or 8%.

Absolute risk difference

The difference in absolute risk of an outcome between the control group and the treatment group, or between two treatment groups. An absolute risk difference of zero indicates no difference between the groups.

Example: The absolute risk difference between the groups is $0.1 - 0.08 = 0.02$, or 2%.

Number-needed-to-treat (NNT)

The number of people that need to be treated for a given period of time with one treatment instead of another treatment for one additional person to benefit in the outcome of interest. NNT is the reciprocal of absolute risk difference.

Example: The NNT is $1/0.02 = 50$. This means that to prevent one stroke you would need to treat 50 people for 1 year with the new drug, rather than control treatment.

Relative risk (or risk ratio)

The ratio of how often an event occurs in two groups receiving different treatments. A relative risk of 1.0 indicates no difference between the groups.

Example: The relative risk of stroke with treatment compared to control is $0.08/0.1 = 0.8$, or 80%.

Relative risk difference

Difference between the relative risk and no effect ($1 - \text{relative risk}$).

Example: The relative risk difference is $1 - 0.8 = 0.2$, or 20%. In other words, treatment reduced the risk of stroke by 20% compared to the control group.

Confidence interval

The range of values within which the true value for the whole population represented by the study patients is likely to lie. For example, when the confidence interval for a relative risk includes 1.0, this is interpreted as no evidence of a difference between groups.

Example: The point estimate and 95% confidence interval for the relative risk of stroke with treatment is 0.8 (0.4–1.7).

This means that the risk of stroke in the treatment group might be as low as 40% of the risk in the control group, or may be 70% more than in the control group. In this case, the results of the study do not help us to decide whether to offer the treatment to patients.

Intention-to-treat analysis

Analysis of patient outcomes based on their randomised group, regardless of whether they actually received the planned intervention. Avoids bias associated with non-random loss of participants from treatment groups.

Power

A study's ability to detect a statistically significant difference between the control and experimental groups. Factors that determine a study's power include its size, the number of outcomes that occur (e.g. strokes) and the smallest difference in outcomes between the therapy and the control groups that is considered to be clinically important.

Surrogate measure

A laboratory or physiological variable that is used as a substitute for a more clinically meaningful endpoint that defines how a patient functions or survives. For example, bone density for fracture, cholesterol for myocardial infarction, and blood pressure for stroke. Surrogates are usually measured relatively quickly and easily, so are used when observing clinical outcomes would require long follow-up.

Generalisability (or external validity)

The ability to apply the findings of a study to other circumstances.

Health economics terms

Cost-benefit analysis

Values all costs and outcomes in monetary terms.

Cost-effectiveness analysis

Describes the difference in costs and benefits of therapies with a common health outcome (e.g. blood pressure reduction). Results are presented as a ratio (e.g. cost per event prevented, cost per unit of blood pressure lowered).

Cost-minimisation analysis

An analysis conducted when two treatments are assumed to be equivalent and only costs are compared.

Cost-utility analysis

Expresses the effects of therapies as life-years adjusted by people's preferences, so includes length and quality of life. Usually expressed as cost per QALY (quality-adjusted life-year). Useful when therapies being compared have a wide range of outcomes and a common unit of measurement is needed.

Economic evaluation

Identifies and measures the costs and consequences associated with alternative health interventions. A generic term for cost-benefit, cost-effectiveness, cost-minimisation and cost-utility analyses.

Incremental cost-effectiveness ratio

The ratio generated by a cost-effectiveness analysis. Expresses the differences in costs and effects of therapies (i.e. $\text{cost A} - \text{cost B} / \text{effect A} - \text{effect B}$).

Modelling

Applies evidence from randomised trials to 'real-life' settings to better judge a drug's clinical and economic performance. May be used to extend surrogate outcomes (such as blood pressure reduction) to clinical endpoints (cardiovascular events prevented), to extend findings of study beyond duration to likely duration of use and to examine the impact of differences between study subjects and patients likely to receive the drug in clinical practice.

Quality-adjusted life-years (QALYs)

A measure of health status that includes both duration and quality of life.

Sensitivity analysis

Assesses how robust an analysis is to uncertainty in or assumptions about the data or methods used by testing how much the result changes when important parameters are varied.

* Bibliography available on www.npsradar.org.au