

To prescribe or not to prescribe: issues surrounding our approach to new drugs

New drugs are often perceived as more effective and safer than older drugs and, supported by clever marketing, may quickly become widely used. But is there any basis to this assumption of superiority, or are there potential pitfalls to such enthusiastic acceptance? This *NPS News* highlights issues you should consider before accepting a new drug into your routine prescribing.

Approximately 30 new drugs have been marketed in Australia in the last 12 months¹ (not including new presentations or generic versions of available drugs). When considering a new drug, the prescriber needs to balance the advantages the new drug purports to offer against the risks of unknown effects. Asking the following questions when assessing new drugs can help achieve this balance.

Where does the new drug fit into the overall clinical management of the disease?

This is generally a difficult question to answer in the initial stages of a drug's marketed life as the volume of evidence required to make an informed assessment is not available. In deciding the worth of the new drug, consider:

- Does this drug show real advantages over current therapies?
- Do the benefits from this drug outweigh the risks involved?
- Are there some patients who may particularly benefit from this drug?

Is the new drug a genuine advance or a 'me-too'?

Many drugs are merely new members of an already existing drug class (often called 'me-too' drugs) and do not significantly add to the range of drugs available. For example, one could quite justifiably ask 'do we really need eight ACE inhibitors?' Only a limited number of truly novel drugs with distinct pharmacology are developed each year. Occasionally,

development within a class can be valuable; for example, the cardioselective properties of metoprolol were an advance on propranolol.

How safe is this drug?

Most pre-marketing studies are designed and powered to detect efficacy rather than safety. Furthermore, these clinical trials carefully select patients, often with only the condition of interest (thus being unrepresentative of the general population), and generally in numbers smaller than those needed to detect rare adverse effects.

The incidence and severity of rare adverse effects may only be uncovered after using the drug in large numbers of patients. These results may lead to a reassessment of the benefit/risk profile of the drug. Recent examples of this are the drug interactions with mibefradil (Posicor[®]) that caused cardiac arrhythmias, and hepatotoxicity with troglitazone (Rezulin[®]); in both cases these discoveries led to the withdrawal of the drug from the market.

Experience with the class of drugs a new drug belongs to is no guarantee of safety: trovafloxacin (Trovan[®]) was withdrawn because of adverse effects despite good safety records with the other quinolone antibiotics available.

Reporting suspected adverse effects with a new drug to the Adverse Drug Reactions Advisory Committee (ADRAC) assists in defining a fuller safety profile. However, it is acknowledged that substantial under-reporting is common with spontaneous, postmarketing surveillance systems. Consequently, it can take some time before an obscure but serious adverse event occurs in sufficient numbers to be detected and for suspicions to be raised.

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How effective is this drug?

Are claims substantiated with the best possible evidence?

The best evidence usually comes from randomised controlled trials of sufficient sample size with appropriate measures of effect. The duration of the clinical trial should be representative of the condition being treated—does a 24-week trial of a drug used in Alzheimer's disease tell us much about the long-term effects of treating the condition?

Has the new drug been compared with existing therapies at effective doses?

Head-to-head comparisons with standard therapies are often lacking at the time a new drug is marketed. Placebo comparisons are often required by regulatory authorities but may not be useful in identifying the place in therapy of a new drug.

Do data relate to the drug's impact on clinical outcomes or only to surrogate measures of efficacy?

Data on new drugs commonly relate to surrogate measures of efficacy (e.g. lowering blood pressure)

rather than their impact on clinical outcomes such as morbidity and mortality. Older drugs are more likely to have data describing their effect on morbidity and mortality as this information accumulates with time.

If you need more information on new drugs

Information on a new drug can be obtained from:

- the approved product information (and consumer medicine information) which is a comprehensive distillation of a drug's properties
- *Australian Prescriber* which includes a section on new drugs in each issue
- the NPS Therapeutic Advice and Information Service (TAIS) that has been established to provide timely drug information to health professionals (phone: 1300 138 677)
- *Australian Medicines Handbook* which includes monographs on new drugs considered likely to become available within the lifetime of the edition published.

Zolpidem (Stilnox®) – is it better than a benzodiazepine hypnotic?

Zolpidem has been available overseas for some time. It is approved in Australia for the short-term treatment of insomnia in adults. It is claimed that, at the recommended dosing regimen, tolerance does not develop and that rebound insomnia or withdrawal symptoms are not a problem after discontinuation.

Many of the problems identified with hypnotic benzodiazepines (dependence, tolerance, withdrawal symptoms, rebound insomnia) can be minimised by using these drugs judiciously, ensuring the lowest effective dose is used for a short-term period only (e.g. 2–4 weeks).

When used at approved doses and for short periods of time, there appears to be little difference in either efficacy or tolerability

between zolpidem and benzodiazepine hypnotics such as triazolam.² Unfortunately, many people with chronic insomnia are likely to use hypnotics for extended periods of time. In common with benzodiazepines, there have been reports of abuse, tolerance and withdrawal associated with zolpidem.^{2,3}

The subjective nature of many of the measures of efficacy and tolerability in insomnia trials makes it difficult to interpret the results reliably. Long-term experience is required before firm conclusions can be made regarding any clinical advantages zolpidem may have over benzodiazepines.

Considering its greater costs, there seems little motive to prescribe zolpidem preferentially to a benzodiazepine at present.

We are all individuals

There is considerable interpatient variability in the dose–response relationship for a drug. As a result, dose tailoring is required to establish effective doses of a drug in each patient without causing undue adverse effects. In establishing an effective dose, initiate therapy at a low dose and titrate according to response.

Remember...

A drug may be approved for **first-line** therapy but this does not necessarily mean that its use as **first choice** is appropriate.

Fixed-dose combinations not to be used to initiate therapy

Fixed-dose combinations should not be used to initiate therapy. Rather, slow titration of the individual drugs to an effective and tolerated dose is advised. If the established effective doses for the individual drugs correspond to those that are present in a combination product, it is reasonable to substitute the combination on the grounds of cost and potentially improved compliance.

With some exceptions (combined oral contraceptives, levodopa-containing preparations for Parkinson's disease, and a few antibiotic examples), Australia has traditionally spurned combination therapies, considering them at odds with some of the principles of rational prescribing.

Recently a number of fixed-dose combinations have been approved for use in Australia, including antihypertensive combinations of a low-dose thiazide diuretic with either an ACE inhibitor or an angiotensin II receptor antagonist, and an inhaled anti-asthmatic combination.

Combination products contain **two or more** drugs. Polypharmacy issues relating to side-effects and drug interactions will be relevant.

Arguments against fixed-dose combinations

- Modifying the dose of a single component of the combination cannot be achieved by adjusting the dose of the combination product.⁴
- The evaluation of adverse drug reactions is complicated by the combination as identifying the offending agent becomes less clear.⁴
- Occasionally, the pharmacokinetics of the various components are different so that a particular dosing regimen can either underdose or overdose one of the components⁴; for example, when the analgesic combination of paracetamol and dextropropoxyphene (Capadex®, Di-Gesic®) is dosed 4–6 hourly based on paracetamol analgesia, dextropropoxyphene can accumulate because of its longer half-life and may cause side-effects.

When a patient asks for the new 'wonder drug'

Good communication is required to address patient expectations created by the media hype surrounding a new drug. Discussing the goal of therapy, treatment options and the evidence supporting these treatments with the patient is an

important step toward facilitating informed choice and understanding the management strategy. The consumer medicine information (CMI) for a drug can be a useful tool to initiate discussion.

Bupropion (Zyban®) for smoking cessation

Bupropion is not a new drug; it has been used as an antidepressant for more than a decade overseas. What is new is its application to help people stop smoking. Public interest in this drug caused demand to outstrip supply soon after it became available on the Pharmaceutical Benefits Scheme (PBS). Was this rush by smokers keen to 'kick' the habit met by prescribing based on sound evidence of superior efficacy to what was already available?

Bupropion has been assessed only in settings that provided regular counselling in subjects who were highly motivated to quit.^{5,6} There is no evidence that bupropion used in isolation is effective.

In terms of efficacy, bupropion was superior to placebo in a randomised controlled trial of smoking cessation. However, given we know anecdotally what poor results 'going cold turkey' achieve, being better than placebo is the minimum that should be expected from a smoking cessation agent.

To date, the only trial comparing bupropion with nicotine replacement therapy (NRT)

found bupropion was more effective than an NRT patch⁷; this needs to be confirmed by other studies and with other forms of NRT.

Insomnia and dry mouth are common with bupropion while serious adverse effects, such as seizures, angioedema, and serum sickness-like reactions, have been reported. Adverse effects with NRT are usually minor and transient, particularly when the dose is matched to the level of smoking.

There is currently insufficient evidence to recommend one treatment over the other based on efficacy. However, given extensive experience with NRT and its preferred safety profile, it is reasonable to consider treatment with NRT before bupropion for smoking cessation,⁶ despite the greater costs to the patient.

It should be remembered that pharmacotherapy for nicotine addiction should be an adjunct to counselling and support services such as the Quitline (tel: 131 848).

Drug regulation: from new drug application to the prescription pad

Below is a brief representation of the main processes of drug regulation in Australia.

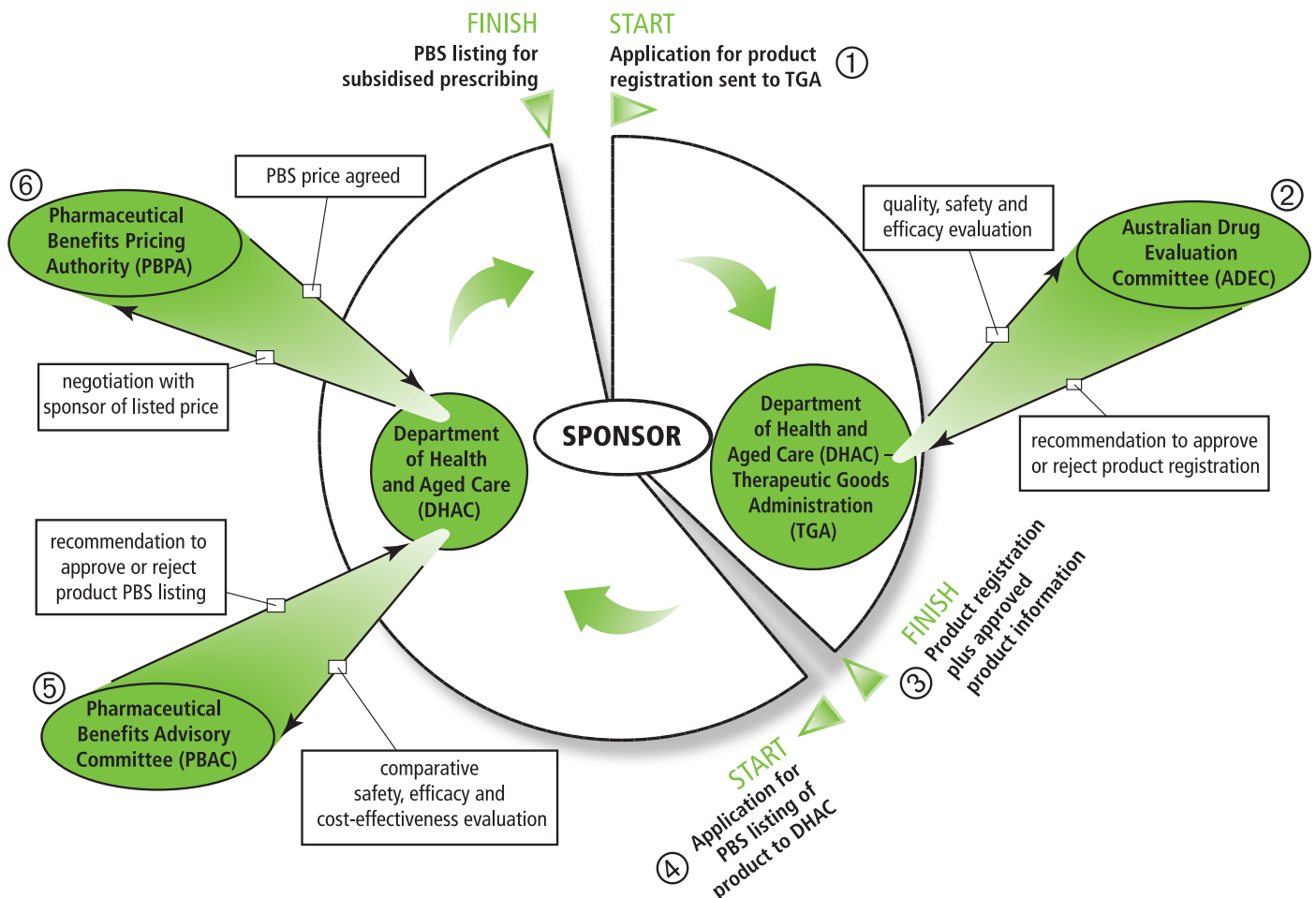


Diagram is a simplified schematic representation of the process.
The time taken for individual applications to move through the system does differ.

How it works

1. A sponsor (usually a pharmaceutical company) applies to the Therapeutic Goods Administration (TGA) to register a new drug, a new presentation of an existing drug, or a new indication for an existing drug, for use in Australia.
2. The Australian Drug Evaluation Committee (ADEC) advises the TGA on the quality, safety and efficacy of the new drug application.
3. Once approved by the TGA, the pharmaceutical company can market the new drug for its approved indications. At this stage, the drug can be prescribed by GPs on private prescriptions only.
4. The pharmaceutical company may decide to apply to the Department of Health and Aged Care for listing on the Pharmaceutical Benefits Scheme (PBS).
5. The Pharmaceutical Benefits Advisory Committee (PBAC) advises the Minister for Health and Aged Care on the comparative safety, efficacy, cost-effectiveness, and clinical role of the new drug relative to existing therapies on the PBS.
6. If PBS listing of the drug is recommended, the pharmaceutical company negotiates the PBS-listed price with the Pharmaceutical Benefits Pricing Authority (PBPA).

The PBS listing of a new drug allows Commonwealth-subsidised prescribing of the new drug for those indications listed in the Schedule of Pharmaceutical Benefits (yellow book) only. PBS-listed indications may be a subset of the approved indications for the drug; there is no subsidy for drugs used for indications which are not listed on the PBS.

What's new?

New in January—Australian Medicines Handbook Edition 3, 2002

Since 1998 the AMH has provided readily accessible, concise, current, independent drug information for Australian health professionals.

Comprehensively updated for the 3rd edition:

- **More than 70 new drugs**
- **New and expanded therapeutic areas**
- **New evidence incorporated throughout, for example:**
 - Hormone replacement therapy is not effective in primary prevention of cardiovascular disease, and is possibly associated with early excess mortality when used for secondary prevention.
 - Impact of new trials for calcium channel antagonists: diuretics and beta-blockers still first-line for uncomplicated hypertension.
- **Role of new drugs explained, for example:**
 - New antidiabetic agents (rosiglitazone, pioglitazone, repaglinide): no established effect on diabetes-related morbidity and mortality.

The new AMH uses lighter, high quality paper—giving you more information in a smaller book. Special pre-publication offer until 10 January 2002, telephone AMH on 08 8222 5861, fax 08 8222 5863.

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RACGP guidelines for benzodiazepine use

The Royal Australian College of General Practitioners (RACGP) has reorganised their web site. The updated version of the RACGP guidelines for the rational use of benzodiazepines referred to in *NPS News 16, Focus on psychogeriatrics*, can now be found at <http://www.racgp.org.au/document.asp?id=510>.

Or you can go to their home page, <http://www.racgp.org.au>, and follow the pathway: Our Publications ► Guidelines ► Benzodiazepines.

National Medicines Symposium 2002

- How is the Quality Use of Medicines movement influencing prescribing in Australia?
- What is happening at both the local and policy levels that can be of use to GPs, pharmacists and other health professionals?
- What impact will current research and evaluation have on the direction of Quality Use of Medicines?

These are some of the questions that will be tackled at the National Medicines Symposium 2002, Linking people, actions and policy for Quality Use of Medicines to be held at the:

National Convention Centre, Canberra Wednesday 20 – Friday 22 March 2002

If you would like information or to register, please contact: Conference Solutions: Telephone: 02 6285 3000
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1. National Prescribing Centre. MeReC Bulletin 1998;9(6):21–4
2. Martin RM. Aust Prescr 1998;21:67–8

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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 individual clinical circumstances of each patient.



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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

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