

## Inside ▶

Rofecoxib: a case in point

Knowing what we don't know

What should we do?

Talking to consumers about new drugs

## Mind the gaps: how much do we really know about new drugs?

Drug marketing focuses on what is known about new drugs. An important part of deciding whether to use a new drug is being aware of what isn't known.

### Rofecoxib: a case in point

The recent withdrawal of rofecoxib (Vioxx) highlights the limitations of the evidence for new drugs. The lower risk of gastrointestinal toxicity with COX-2 selective NSAIDs compared to conventional NSAIDs led to their rapid uptake, despite concerns raised in 2000 by the VIGOR study<sup>1</sup> that rofecoxib increased the risk of cardiovascular events. It was only in October 2004 that the increased risk of heart attack and stroke was confirmed and rofecoxib was suddenly withdrawn.<sup>2</sup> Figure 1 shows how the safety evidence for rofecoxib accumulated.

A risk of using any new drug is the potential for unknown adverse effects. Most clinical trials conducted for registration are limited in their ability to detect rare or long-term adverse events because they

- use relatively small sample sizes
- use short treatment durations
- tend to include highly selected patients who do not reflect the wider population in which the drug will eventually be used.

As a result, serious adverse effects often emerge after new drugs are marketed. One US study showed that 10% of drugs approved between 1975 and 1999 had serious safety warnings added after approval, and 3% were withdrawn from the market.<sup>3</sup>

For information about switching from rofecoxib, see the factsheet on the NPS website ([www.nps.org.au/resources/content/nps\\_factsheet\\_vioxx\\_20041001.pdf](http://www.nps.org.au/resources/content/nps_factsheet_vioxx_20041001.pdf)).



**Figure 1: Accumulating evidence of the cardiovascular risk of rofecoxib.**

#### 1999: Rofecoxib first available

- Data from 5435 patients exposed to rofecoxib. Most patients had received it for less than 6 months. Placebo comparisons were restricted to 6-week studies.<sup>4</sup>
- Low overall incidence of thromboembolic events in groups receiving rofecoxib, conventional NSAID or placebo.<sup>4</sup>



#### 2000: VIGOR study published<sup>1</sup>

- Found a significantly higher incidence of myocardial infarctions amongst patients treated with rofecoxib 50 mg/day than those treated with naproxen 1000 mg/day (0.4% vs 0.1%).<sup>1</sup>
- Not clear whether this result was due to a prothrombotic effect of rofecoxib, a cardioprotective effect of naproxen, or both.



#### 2000–2004: Epidemiological studies and postmarketing surveillance

- Various analyses of cardiovascular events associated with rofecoxib during post-marketing use and clinical trials\* were published.<sup>5–9</sup>
- Spontaneous adverse event reporting had limited ability to detect the elevated risk because of the relatively small increase in risk against a high background rate of cardiovascular events.<sup>4</sup>



#### 2004: Rofecoxib withdrawn

- APPROVE, a large placebo-controlled study, found that after 18 months, people taking rofecoxib 25 mg had an increased risk of cardiovascular events (mainly heart attacks and strokes) compared to people taking placebo. Absolute event rates were 0.75 events per 100 patient-years for placebo and 1.48 events per 100 patient-years for rofecoxib.<sup>10</sup>

\*These trials were designed to assess efficacy rather than cardiovascular events.

## Knowing what we don't know

In light of the inevitable gaps in the evidence, a cautious approach to new drugs is warranted. The following examples illustrate some of the common limitations of the evidence.

### Appropriate comparisons may not be available

Deciding whether to prescribe a new drug means comparing it to existing treatments to determine whether it offers an advantage. Comparing the efficacy of new drugs with existing therapies is often hampered by the lack of appropriate head-to-head studies. A recent survey found that 25% of new drugs registered in France in 2000 and 2001 had no appropriate comparisons with current treatments.<sup>1</sup>

Even when comparative studies are available, they may not tell us what we need to know. For example, they may compare surrogate measures (such as cholesterol lowering) rather than clinical outcomes (such as the effect on the risk of coronary events). Some studies may not be powered to permit conclusions to be drawn about

the comparative efficacy of active treatments, or may compare drugs at non-equivalent doses.

The results of some clinical trials may never be publicly available—studies with unfavourable results may not be submitted for publication, and medical journals may be less interested in publishing negative or inconclusive studies.

In an attempt to promote transparency of clinical trial reporting, the International Committee of Medical Journal Editors recently announced that only clinical trials registered in a public repository before patient enrolment begins would be published by member journals, which include *The Lancet*, *JAMA*, *The New England Journal of Medicine* and *The Medical Journal of Australia*.<sup>2</sup>

### Comparative studies may be unhelpful

Immediate-release **metoprolol** has long been available in Australia for use in hypertension, angina, myocardial infarction and migraine prophylaxis. In 2004, a controlled-release formulation of metoprolol (metoprolol CR–Toprol XL) became available for adjunctive treatment in heart failure.

When added to usual heart failure therapy, metoprolol CR reduces annual mortality risk compared to placebo<sup>3</sup> but there are no outcome trials directly comparing metoprolol CR with other beta-blockers approved for use in heart failure.

Although immediate-release metoprolol and carvedilol have been compared<sup>4–6</sup>, controlled-release and immediate-release formulations of metoprolol are not interchangeable. The largest comparative study of immediate-release metoprolol and carvedilol found significantly lower mortality rates and greater improvement in left ventricular ejection fraction with carvedilol.<sup>6</sup> However, in this trial, the doses of immediate-release metoprolol were less than equivalent to the recommended doses for metoprolol CR, making it difficult to anticipate the comparative efficacy of the controlled release formulation and carvedilol.

### Useful information may be inaccessible

**Aripiprazole** (Abilify), a new antipsychotic, was listed on the PBS in May 2004. Five placebo-controlled clinical studies had been conducted<sup>7</sup>, four of which included an active treatment arm: risperidone in one study and haloperidol in three studies. Risperidone and haloperidol were used to confirm the responsiveness of the study population to active treatment but the studies did not include enough patients to allow statistical comparison of the efficacy of aripiprazole and the other antipsychotics.

Clinical trial registers indicate that comparative studies of aripiprazole and olanzapine have been done<sup>8</sup>, but the results are yet to be fully published.

In the absence of access to comparative data, it is impossible to determine how the efficacy of aripiprazole compares to existing antipsychotics.



## Clinical trials do not usually define safety profiles

The example of rofecoxib demonstrates that the full safety profile of a new drug may not be established when the drug becomes available. Postmarketing reports

of adverse events can be critical in determining the safety of new drugs, as experience with the 'glitazones' has shown (see below).

### Postmarketing surveillance can reveal unknown side effects

**Troglitazone** was available only briefly before being withdrawn because it caused serious liver damage. In clinical trials with troglitazone, some cases of elevated liver enzymes and drug-associated hepatitis occurred. However, it was only once the drug was more widely used that the extent of the problem became apparent. Many cases of acute liver failure, some of which were fatal, were reported leading to the drug's withdrawal in March 2000.<sup>9</sup>

The experience with troglitazone led to heightened awareness of the potential for liver toxicity with pioglitazone (Actos) and rosiglitazone (Avandia). Liver function tests are recommended for patients taking pioglitazone or rosiglitazone at baseline, every 2 months for the first 12 months, then periodically thereafter.<sup>10,11</sup> Postmarketing surveillance has so far not revealed a similarly widespread problem with pioglitazone and rosiglitazone. However, some cases of liver problems have been reported with both drugs.<sup>12</sup>

## ? What should we do?

### Approach new drugs with caution

Be aware of the gaps in the evidence. Use a new drug only when it has an advantage over existing treatment. Where new and older drugs appear to have similar benefit-harm profiles, use the drug with the better known safety profile.

See *NPS News 31: New (and old) ways of looking at new drugs* for a checklist of questions to ask about new drugs (see [www.nps.org.au](http://www.nps.org.au), go to Health Professionals, then Newsletter Index in the left-hand panel).

### Use evidence-based sources of information

*NPS RADAR (Rational Assessment of Drugs and Research)*

- Provides updates on new drugs as they are listed on the PBS. Register for free email updates by visiting [www.npsradar.org.au](http://www.npsradar.org.au).

*Australian Prescriber*

- New drugs section on the website ([www.australianprescriber.com](http://www.australianprescriber.com)) and in each bimonthly issue considers the merits of drugs recently made available in Australia.

*Australian Medicines Handbook*

- From January 2005, one new drug monograph will appear on the AMH website ([www.amh.net.au](http://www.amh.net.au)) every 3 months. New drugs monographs will be included in AMH on CD and the web every 6 months, and annually in the paper version.

*Therapeutic Guidelines*

- Books reviewed every 2–3 years. Electronic version (eTG) updated quarterly. For more information, go to [www.tg.com.au](http://www.tg.com.au).

### Report all suspected adverse reactions to new drugs

See the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)) for details on how to report adverse reactions.

Keep an eye on the *Adverse Drug Reactions Bulletin*. The *Bulletin* flags emerging safety issues and lists 'Drugs of Current Interest' for which all suspected adverse reactions should be reported. It is distributed with *Australian Prescriber* and is available at [www.tga.gov.au/adr/aadrb.htm](http://www.tga.gov.au/adr/aadrb.htm).

## Talking to consumers about new drugs

The questions you might ask yourself when deciding whether to use a new drug are just as relevant to consumers. Discussing how the new drug compares to current therapy in terms of efficacy, safety, cost and convenience can help to clarify whether the new drug offers any advantage and demonstrate the limitations of the available evidence.

### Questions to ask about new drugs

- Has the new medicine been shown to be more effective than the current choice in terms of an outcome that is meaningful to patients?
- How much is known about the safety of the new medicine?
- What is the cost of the new medicine to patients and the community? If on the PBS, are there any restrictions on prescribing?
- Is the new medicine convenient to use?

### Consumer-friendly information about new drugs

#### NPS RADAR for Consumers

- Will soon be available on the RADAR website ([www.npsradar.org.au](http://www.npsradar.org.au)).
- Explains PBS eligibility and important quality use of medicines issues for new drugs.

#### Consumer Medicine Information (CMI)

- Available in prescribing and dispensing software, eMIMS, APP Guide and from pharmaceutical companies.
- A selection of CMI is available on the NPS website ([www.nps.org.au](http://www.nps.org.au), go to Consumers, then Consumer Medicine Information in the right-hand panel).

#### Australian Prescriber

- Selected articles include a 'Comment for Consumers'. See [www.australianprescriber.com](http://www.australianprescriber.com).

### Coming soon—NPS RADAR for Consumers

NPS RADAR for Consumers describes the place in therapy of new drugs, how they compare to existing treatments, and highlights important information about safety and dosing. RADAR for Consumers also provides simple explanations of complicated PBS listings. Other sources of consumer-friendly information about new drugs are listed above.



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#### Knowing what we don't know

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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.*



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