

## Coax, COX and cola

*Manufacturers' claims in well funded marketing campaigns cannot replace the test of time*

DECLARING WAR AND PRESCRIBING DRUGS are decisions dependent on information, and the consequences can be calamitous if that information is incomplete or inaccurate.

The calamity which threatened the sustainability of the Pharmaceutical Benefits Scheme (PBS) in 2000 and 2001 was the volume of prescriptions for cyclooxygenase (COX)-2 inhibitors. Celecoxib was listed on the PBS on 1 August 2000, and by the end of December 2000 over 1.5 million prescriptions had been written, costing the government more than \$76 million.<sup>1</sup> By the end of June 2001, the cost had exceeded \$160 million.<sup>2</sup>

In this issue of the *Journal (page 403)*, Kerr and colleagues confirm the rapid rise in prescriptions for celecoxib and rofecoxib.<sup>3</sup> However, their research cannot explain why the general practitioners in their study were so enthusiastic about the new drugs. The doctors' decisions to prescribe would have been based on the available information. At the time the drugs were launched in Australia, most of that information would have been supplied directly or indirectly by the manufacturers. There was little independent information, and the major randomised trials of celecoxib (CLASS<sup>4</sup>) and rofecoxib (VIGOR<sup>5</sup>) were only published in late 2000.

The information from the manufacturers emphasised the relative safety of the new drugs. Compared with non-selective non-steroidal anti-inflammatory drugs (NSAIDs), the new drugs caused fewer peptic ulcers. This was an important message, as doctors are often warned about the serious gastrointestinal complications of NSAIDs.

There is evidence that some patients were prescribed the new drugs because they had suffered adverse effects from NSAIDs.<sup>6</sup> However, this did not result in a fall in the prescribing of NSAIDs. The availability of celecoxib and rofecoxib increased the number of people being treated for musculoskeletal disorders,<sup>3</sup> suggesting the new drugs were being prescribed for conditions beyond the restrictions of the PBS. Such conditions include non-specific back pain, sprains and sports injuries.<sup>3,6</sup>

Some general practitioners believe that COX-2 inhibitors are more effective than NSAIDs.<sup>6</sup> This belief is not confirmed by the clinical trials, and now even the evidence of their improved safety is being questioned.<sup>7</sup> The published results of VIGOR<sup>5</sup> and CLASS<sup>4</sup> did not include all the data submitted to the United States Food and Drug Administration (FDA).<sup>7,8</sup> The favourable results of CLASS were based on only the first 6 months of the trial. Analysis of the 12 months' data that was available to the FDA suggests that celecoxib was associated with a similar number of ulcer complications as were diclofenac and ibuprofen.<sup>7,9</sup> Similarly, analysis of the complete data for rofecoxib suggests it may be associated with an increased risk of cardiovascular events<sup>10</sup> and that serious adverse effects may be more frequent than with naproxen.<sup>8</sup>

The Therapeutic Goods Administration (TGA) probably had access to the complete data when it evaluated the drugs for use in Australia. However, unlike the FDA data, which are published on its website,<sup>8,10</sup> the TGA's evaluations are kept secret. Would publication of the TGA's evaluations

have alerted Australians to the possible problems with COX-2 inhibitors?

Concerns about the drugs only arose months after they were marketed. Even if they had been aired earlier, they are likely to have been lost in the excitement surrounding the launch of the drugs. Even the Minister for Health and Aged Care put out a press release listing some of the benefits of celecoxib and describing it as a “major breakthrough in arthritis therapy”.<sup>11</sup>

Enthusiasm for the COX-2 inhibitors waned slightly with experience. In Kerr and colleagues’ study, rofecoxib was not embraced to the same extent as celecoxib. Nearly a third of the patients prescribed rofecoxib had previously been prescribed celecoxib, suggesting they had been disappointed by the response.<sup>3</sup> Initial enthusiasm followed by a slower increase or plateau in prescribing is a common pattern with new drugs. If the new drugs are not as good as they were thought to be, can they justify being twice the price of other NSAIDs?

What coaxes doctors to expose their patients to new products when so little information is available? I believe that manufacturers’ marketing strategies play on doctors’ desire to give their patients the best possible care. Much of the variation in the prescribing of new drugs depends on the personality of the doctors, and probably on their susceptibility to these marketing techniques.<sup>12</sup> The prospect of reduced adverse effects is likely to have a strong influence on prescribing practice.

If adopting new drugs quickly actually puts patients at risk, prescribers must be presented with information to balance the claims of the drug companies. Achieving this balance is difficult, partly because independent information (such as *Therapeutic guidelines* and the *Australian medicines handbook*) sometimes comes at a cost, while drug company information — supported by massive advertising budgets — is free. In 2000, the amount spent on promoting rofecoxib to Americans (US\$160 million) exceeded the advertising budgets for Pepsi and Budweiser beer.<sup>13</sup>

In view of the popularity of the new drugs in the United States, perhaps Australia should have been prepared for the demand. If the TGA had been able to provide its evaluations to publishers of independent information, they could have prepared prescribing guidelines before the drugs were marketed.

The National Prescribing Service has recently received funding to provide doctors with independent information about new additions to the PBS. To ensure advertising does not swamp these messages, perhaps there should be limits on promotional activities around the date of PBS listing. While governments are unlikely to ban advertising, they could at least mandate that it provides quantitative information about the outcomes for patients.<sup>14</sup>

Another approach to new drugs is not to use them. This will spare patients from the serious adverse effects which sometimes only emerge after marketing. The Health Research Group in the US now recommends waiting 7 years before using a new drug that provides no clear advantage over current therapies.<sup>15</sup> While this may be an extreme

position, there is no need to feel pressured into immediately prescribing the latest drug. New is not always better.

**John S Dowden**

Editor in Chief  
Australian Prescriber, Canberra, ACT  
jdowden@nps.org.au

*Competing interests:* Australian Prescriber is published by the National Prescribing Service. John Dowden is an unpaid director of Therapeutic Guidelines Ltd, and a member of the Editorial Advisory Board of *Australian Medicines Handbook*.

1. Analysis section. Pharmaceutical Benefits Branch. PBS expenditure and prescriptions January 2000 to December 2000. Available at: [www.health.gov.au/pbs/pubs/pbbexp/pbdec00/](http://www.health.gov.au/pbs/pubs/pbbexp/pbdec00/) (accessed Sep 2003).
2. Pharmaceutical Benefits Pricing Authority. Annual report for the year ended 30 June 2001. Canberra: AGPS, 2001.
3. Kerr SJ, Mant A, Horn FE, et al. Lessons from early large-scale adoption of celecoxib and rofecoxib by Australian general practitioners. *Med J Aust* 2003; 179: 403-407.
4. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study. A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000; 284: 1247-1255.
5. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000; 343: 1520-1528.
6. Cutts C, LaCase A, Tett S. A clinical audit of the prescribing of celecoxib and rofecoxib in Australian rural general practice. *Br J Clin Pharmacol* 2002; 54: 522-527.
7. Juni P, Rutjes AW, Dieppe PA. Are selective COX-2 inhibitors superior to traditional non-steroidal anti-inflammatory drugs? *BMJ* 2002; 324: 1287-1288.
8. Budenholzer BR. Rofecoxib did not provide unequivocal benefit over traditional NSAIDs [letter]. *BMJ* 2002; 325: 161.
9. Hrachovec JB, Mora M. Reporting of 6-month vs 12-month data in clinical trial of celecoxib [letter]. *JAMA* 2001; 286: 2398.
10. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001; 286: 954-959.
11. Wooldridge M. Relief for half a million arthritis sufferers [media release]. Canberra: Commonwealth Department of Health and Aged Care; 1 June 2000. Available at [www.health.gov.au/mediarelyr2000/mw/mw20048.htm](http://www.health.gov.au/mediarelyr2000/mw/mw20048.htm) (accessed Sep 2003).
12. Jacoby A, Smith M, Eccles M. A qualitative study to explore influences on general practitioners' decisions to prescribe new drugs. *Br J Gen Pract* 2003; 53: 120-125.
13. National Institute for Health Care Management Research and Educational Foundation. Prescription drugs and mass media advertising 2000. Washington: NIHCM Foundation, 2001.
14. Loke TW, Koh FC, Ward JE. Pharmaceutical advertisement claims in Australian medical publications. *Med J Aust* 2002; 177: 291-293.
15. Health Research Group. New research results on safety of newly approved drugs causes Health Research Group to extend five-year waiting rule to seven years. *Worst Pills Best Pills* 2002; 8: 41-43. □