



Are new drugs as good as they claim to be?

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Approval of new drugs by the Therapeutic Goods Administration is no guarantee that they are superior or even equivalent to drugs already on the market. The drug evaluation process only assesses quality, safety and efficacy, not the therapeutic value of a drug. Assessments of the value of new drugs from Canada, France and the USA all show that at best one third of new drugs offer some additional clinical benefit and perhaps as few as 3% are major therapeutic advances.

Drug companies are spending an estimated \$1–1.5 billion per year promoting their drugs in Australia.¹ One group of drugs that are heavily promoted as being better than existing products are single enantiomers of drugs that were initially introduced as racemic mixtures. The two prime examples of this phenomenon are esomeprazole which is the S-enantiomer of racemic S,R-omeprazole, and escitalopram which is the S-enantiomer of racemic citalopram. Evaluation of both new products has not demonstrated any advantages in safety or effectiveness, over their respective racemic mixtures at appropriate doses.^{2,3} The main reason for bringing both to market seems to have been the imminent expiry of the patents of the original products which would result in generic competition and a significant loss of market share.

In this issue...

The launch of the bright new design of *Australian Prescriber* is an appropriate time to consider the glossy world of advertising. Joel Lexchin tells us that new drugs do not always live up to the promises of marketing campaigns, and Agnes Vitry comments on the insidious growth of advertising drugs to the public. Fortunately, Medicines Australia has imposed sanctions on companies which have breached the advertising code of conduct for prescription drugs.

Patients want information not advertising, so Christopher Newell gives advice on how to find a support group, while Anne Robinson and Susan Day tell us how to look for medical evidence electronically.

An area where the medical evidence may be confused is the interaction of paracetamol and alcohol. Garry Graham, Kieran Scott and Ric Day conclude that paracetamol is still a suitable analgesic for heavy drinkers.

The COX-2 inhibitors are another example of heavy promotion of drugs with questionable advantages. Within nine months of celecoxib coming onto the Australian market there were 2.9 million prescriptions written at a cost of over \$100 million to the Pharmaceutical Benefits Scheme. Their main selling point has been their alleged superior safety. On closer examination, these claims become more difficult to justify. A meta-analysis of morbidity and mortality outcomes in clinical trials shows that the incidence of serious adverse events including death, admission to hospital, and any life-threatening event or event leading to serious disability, was significantly higher with COX-2 selective NSAIDs compared with non-selective NSAIDs.⁴

Premarketing clinical trials are typically placebo-controlled so they do not yield any comparative information. The French drug bulletin *La revue Prescrire* has recently researched the lack of comparative trials by looking at all the new drugs it had evaluated in 2000 and 2001. The researchers selected the indications for which there was at least one reference treatment available that was recommended in consensus statements and whose efficacy had been documented in strict comparative trials. For 80 such indications, 25% of the new drugs were licensed without any comparison with a reference treatment.

Even when comparative trials exist they may be too small or short to provide any meaningful conclusions. For example, when cisapride was marketed in Canada there were nine published randomised controlled trials, but in total only 254 patients were enrolled. Trials with small numbers have at least two major shortcomings: they will almost certainly miss serious, but relatively rare adverse effects, and it is impossible to identify sub-groups of patients in whom the drug may be particularly effective or ineffective. Cisapride has now been completely withdrawn from the market in North America and its use restricted in Australia because of serious adverse effects that only showed up after marketing. Other drugs that are intended for long-term use are often only studied in short-term randomised controlled trials. Short-term trials cannot reliably predict the ultimate benefit, or lack thereof, of drugs that are going to be taken for years. For example, none of the seven trials of losartan that were published when it was introduced in Canada was longer than 26 weeks.⁵

Drug approvals are often based on surrogate end-points,

such as changes in blood pressure or cholesterol. There is a continuing debate about the adequacy of surrogate end-points, but even their defenders concede that the surrogates have not proved to be reliable predictors of outcome in a number of cases.⁶ While journal advertisements are nominally restricted to claims based on these surrogate end-points more expansive claims are often implied. For instance, although cerivastatin was only indicated for cholesterol reduction a 2000 advert in the Australian Family Physician stated that it was as 'strong as an ox' and a 'powerful treatment' possibly leaving the implication that the drug did more than just lower cholesterol.

Finally, there is evidence that data on new drugs which comes from the manufacturer, may be biased. A recent meta-analysis of research analysing the effects of industry funding found that studies funded by pharmaceutical companies were more than four times more likely to produce positive results than those with other sources of sponsorship.⁷

Given the lack of evidence that most new drugs provide any therapeutic advantage over existing treatments, what should general practitioners do? On average, patients will be better off if general practitioners avoid using new drugs until they have been available for more than five years, unless there is strong evidence of superiority over established treatments. Since doctors cannot rely on company promotion to identify this group of drugs, where should they turn? The best sources are the independent drug bulletins and books that not only provide an objective evaluation about individual drugs but also compare drug therapies. Australia is fortunate to have a number of such

sources including *Australian Prescriber*, Therapeutic Guidelines and the Australian Medicines Handbook.

At the very least doctors need to avoid being rushed into using new drugs by siren calls from the pharmaceutical industry.

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Letters

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Dental patients taking warfarin

Editor, –The management of patients taking anticoagulants who require dental extractions is of interest to both medical and dental practitioners.¹ It has been common practice to discontinue anticoagulants to reduce the risk of post-extraction bleeding. Lately however some studies have questioned the need for reduction or withdrawal of warfarin when the INR was within the therapeutic range.

We have recently reported a study involving 70 patients who were taking warfarin for a variety of medical conditions and required dental surgery.² A control group of 35 patients stopped their warfarin before their minor oral surgery while the other patients continued treatment (INR 2–4). Local haemostatic measures were only used when the procedure involved removal of bone or soft tissue surgery.

There was no significant post-treatment haemorrhage in either group. This suggests that patients can safely undergo

minor oral surgical procedures without alteration to their therapeutic anticoagulant regimen. This reduces the risk of thromboembolic episodes occurring when the warfarin is stopped.

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