

### Some sources of independent information

*Australian Prescriber* – [www.australianprescriber.com](http://www.australianprescriber.com)

National Prescribing Service publications: Newsletter, RADAR – [www.nps.org.au](http://www.nps.org.au)

Therapeutic Guidelines – [www.tg.com.au](http://www.tg.com.au)

Australian Medicines Handbook – [www.amh.net.au](http://www.amh.net.au)

There seems to be a glamour about anything new, despite the absence of long-term safety information when a drug is first approved. Of course the industry designs and interprets trials to maximise favourable outcomes. Of course it puts the best possible spin on its marketing messages, but doctors should be smart enough to see through the hype. They need to know that when a drug first appears on the market only limited safety data are available and long-term outcomes, both good and bad, can only emerge with time and appropriately designed, prospective safety studies. It is well established that most prescribers obtain the majority of their information from the pharmaceutical industry and they therefore need more training in how to evaluate the information and what questions to ask drug representatives.<sup>5</sup>

The National Prescribing Service in a recent publication suggests that we should think about what is not known rather than what is known about new drugs.<sup>6</sup> Medical schools and postgraduate colleges must take more responsibility for training students and young doctors about assessing new drugs. This involves more than just an extrapolation of evidence-based medicine. We cannot complacently offload all blame onto government regulators and industry.

Rofecoxib is by no means the first drug to be summarily removed from the market. Cerivastatin and mibefradil suffered a similar fate, in both cases because of fatal toxicity due to interactions with other drugs. There are also many examples of

new drugs which have had significant safety warnings added to their product information within a few years of marketing.

There is no merit in being among the first to prescribe a new drug whatever the pressures from patients and drug companies. It has been well said that 'For all newly-licensed drugs, confidence about safety can only be provisional'.<sup>1</sup> It is essential that both prescribers and consumers grasp this fundamental fact.

### References

1. Summerskill W. Evidence-based practice and the individual. *Lancet* 2005;365:13-14.
2. Vioxx: an unequal partnership between safety and efficacy. *Lancet* 2004;364:1287-8.
3. Peterson WL, Cryer B. COX-1-sparing NSAIDs – is the enthusiasm justified? *JAMA* 1999;282:1961-3.
4. Kerr SJ, Mant A, Horn FE, McGeechan K, Sayer GP. Lessons from early large-scale adoption of celecoxib and rofecoxib by Australian general practitioners. *Med J Aust* 2003;179:403-7.
5. Day R. How to make the most of a visit from a pharmaceutical company representative. *Aust Prescr* 2000;23:97-9.
6. NPS News. Mind the gaps: how much do we really know about new drugs? *NPS News* 2004;37. <http://www.nps.org.au/healthpro> Go to Quick Links, Newsletter Index, No. 37.

### Further reading

Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002;287:2215-20.

Lexchin J. Drug withdrawals from the Canadian market for safety reasons, 1963–2004. *CMAJ* 2005;172:765-7.

*Professor Shenfield is on a number of National Prescribing Service committees, has chaired a writing group for Therapeutic Guidelines, and conducts reviews for the Australian Medicines Handbook.*

## Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

### Expensive new drugs – do we really need them?

Editor, – Professor Moulds' editorial (*Aust Prescr* 2004;27:136–7) suggests that in the last 20 years, new prescription medicines have failed to provide the same therapeutic advances as in the previous 20 years, but are costing significantly more. Furthermore, Professor Moulds believes that patent protection for profiteering pharmaceutical manufacturers is denying the community access to cheaper generic medicines. I would like to dispute the professor on a number of issues.

First, data from the Australian Institute of Health and Welfare show that in the last 20 years, mortality rates have decreased for cardiovascular disease (48%), respiratory disease (33%), and digestive disorders (35%). Medicines have saved more lives in the last 20 years, however morbidity rates have inversely increased.

Secondly, it now costs over \$1 billion for a pharmaceutical company to develop a single new medicine.<sup>1</sup> This is quadruple the cost of 20 years ago. If an innovator cannot recoup these development costs, they have less discretionary

resources to devote to the development of better and more efficacious medicines.

Finally, Australian patent law does not preclude a generic manufacturer from selling a copy of a drug with an expired patent, even if the innovator company advances the development in some way. Nor does Australian patent law allow innovators to make trivial patent applications. 'Evergreening' simply does not exist in Australia and never has.

There is a myth in Australia that generic medicines are cheaper. In reality, generics are cheaper for the government to purchase, but the cost savings have not been passed onto the Australian consumer. Ironically, the government increased the co-payment of Pharmaceutical Benefits Scheme (PBS) items in January 2005 by 21% to make headroom for new and expensive medicines on the PBS.

If we want more effective medicines, we should be encouraging innovation from manufacturers rather than accusing them of being greedy for wanting a return on their investment. The result is that patients who may benefit from a newer and more efficacious medicine will miss out.

Brendan Grabau

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#### Reference

1. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ* 2003;22:151-85.

*Professor R.F.W. Moulds, author of the editorial, comments:*

The main point of my editorial was that new drugs introduced over the last 20 (or so) years have not had the same impact on the practice of medicine as those introduced in the preceding 20 years. The figures quoted by Dr Grabau do not negate the argument. A reduction in mortality from cardiovascular, respiratory and digestive disorders would far more likely reflect the effect of drugs introduced in the preceding 20 years rather than the effect of drugs only introduced in the last 20 years. Regardless of when the drugs were introduced, other factors, such as decreased smoking, may have contributed more to the reduction.

If this argument is correct, then clearly the patent system has not achieved its aim of stimulating the development of important new drugs, so it should be reviewed. The other issues raised by Dr Grabau would presumably be considered in such a review.

#### Polycystic ovary syndrome

Editor, – I note that many people with polycystic ovary syndrome are being prescribed long-term metformin by their general practitioner regardless of any desire to fall pregnant.

I also note that the diagnosis of this syndrome seems to be woollier than a sheep in a lambswool jumper with ugh boots. Even the polycystic part appears to be excluded in some diagnostic criteria, because polycystic ovaries seem to be a feature of chronic anovulation regardless of cause. Yet many people attract the diagnosis on this feature alone with or without being overweight.

I recall a study showing a lack of evidence for cardiovascular risk in these patients and I find that hard to integrate with their insulin resistance. Dr Joyner correctly uses this to continue to prescribe combined oral contraceptive pill to patients over 35, but this sits uncomfortably with me. Could Dr Joyner comment on the quality of this evidence?

If such a person had a BMI > 35 then I would avoid the combined oral contraceptive pill, but this practice is independent of a diagnosis of polycystic ovary syndrome.

Kevin O'Dempsey  
General practitioner  
Brisbane

*Dr B. Joyner, the author of the article, comments:*

As mentioned in my article, polycystic ovary syndrome is a heterogeneous condition. It is a syndrome based on phenotype and there is no single diagnostic criterion. The definitions used in trials may vary depending on the feature being studied. There have also been regional variations in definitions. US definitions have focused on the endocrine features, while definitions from the UK have required the demonstration of polycystic ovaries. There was further revision of the criteria for polycystic ovary syndrome at an international consensus workshop in 2003.<sup>1</sup> If other causes are excluded, two of the following criteria are required:

- oligo- and/or anovulation
- clinical and/or biochemical signs of hyperandrogenism
- polycystic ovaries.

The results of studies regarding the risk of cardiovascular disease in women with polycystic ovary syndrome are conflicting. Most studies have been small and retrospective. Cohorts need to be followed for a longer period of time. However, cardiovascular risk factors including hypertension, diabetes, and hypercholesterolaemia are more common in women with polycystic ovary syndrome, a syndrome that often interweaves with the metabolic syndrome.<sup>2,3</sup>

As mentioned in my article, there is no evidence to suggest women with polycystic ovary syndrome experience more cardiovascular events while on the combined oral contraceptive pill. However, most of the studies have been small and short term. The use of the oral contraceptive pill therefore requires clinical judgement of the harms and benefits for each woman.

## References

1. The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;19:41-7.
2. Wild S, Pierpoint T, McKeigue P, Jacobs H. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. *Clin Endocrinol* 2000;52:595-600.
3. Korhonen S, Hippelainen M, Niskanen L, Vanhala M, Saarikoski S. Relationship of the metabolic syndrome and obesity to polycystic ovary syndrome: a controlled, population-based study. *Am J Obstet Gynecol* 2001;184:289-96.

### Antibiotics for surgical prophylaxis

Editor, – I would agree that the principles set out in the article 'Antibiotics for surgical prophylaxis' (*Aust Prescr* 2005;28:38–40) should be applied to dento-alveolar surgery. However, the suggestions set out in the Dental notes (*Aust Prescr* 2005;28:41) represent a hybrid of traditional dental practice which is not in accord with current evidence-based risk-benefit assessment.

Traditionally in dental practice antibiotics have been given for the prophylaxis of impacted tooth removal after surgery has been completed.<sup>1</sup> This is inappropriate and contrary to the principles of surgical prophylaxis. The suggestion of giving antibiotics either orally or intravenously before the procedure is a step in the right direction, but is not widely currently followed in dentistry. It is also weakened by the suggestion that antibiotics should be continued post-extraction as a matter of clinical judgement.

Current evidence-based studies show that the actual risk of infection after third molar removal is low, of the order of 3–5%. This is similar to the risk of adverse reaction to the penicillins, which are the most commonly used antibiotics for this purpose.

In accordance with the literature, the Oral and Maxillofacial Surgery Unit in Adelaide does not give medically fit patients having dento-alveolar surgery antibiotic prophylaxis. Over the last decade, and many thousands of cases, there has been no increased incidence of infection.

This whole issue is currently being reviewed in depth and will shortly be submitted for publication in the *Australian Dental Journal* and in the new therapeutic guidelines for dental practitioners.

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## Reference

1. Jaunay T, Sambrook P, Goss A. Antibiotic prescribing practices by South Australian general dental practitioners. *Aust Dent J* 2000;45:179-86.

*Associate Professor R.G. Woods, author of the Dental notes, comments:*

I believe the views I expressed in the Dental notes are essentially consistent with the views expressed in Professor Goss' letter. However, Professor Goss and I see things from different backgrounds, Professor Goss from the Oral and Maxillofacial Surgery Unit in Adelaide and myself from general practice in a rural community.

Most third molars I remove appear to communicate, however slightly, with the oral cavity and often appear infected. The mucosal flap and surrounding soft tissues are often the site of a persistent, possibly anaerobic infection associated with eruption. Other teeth requiring removal usually have evidence of long-term infection, an apical bone lesion or loss of supporting alveolar bone.

In reference to my use of the term 'clinical judgement', essentially I refer to pre-operative assessment of the patient including consideration of the reason for the removal of the tooth, whether there is infection and such factors as immunosuppression or any other general condition which may affect recovery. It is my experience that where infection is present, although drainage is achieved by removal of the tooth, recovery is assisted by appropriate antibiotic therapy.

### Varicella vaccine

Editor, – The article 'Frequently asked questions about varicella vaccine' (*Aust Prescr* 2005;28:2–5) notes 'there is a small potential to transmit the vaccine virus ... from direct contact with vesicles'. If a pregnant woman or immunosuppressed patient contacts the vesicles which sometimes appear on a vaccine recipient, is zoster immunoglobulin indicated?

Ina di Paola  
Travel medicine  
Sydney

*Associate Professor Jonathan R. Carapetis, one of the authors of the article, comments:*

There is no definitive answer to this very pertinent question. The main problem lies in deciding whether the rash is vaccine-associated or a potential infection with wild varicella zoster virus that happens to have occurred in the period following immunisation. If it is vaccine-associated, the risk of transmission is incredibly low. I consulted the world's leading expert on the vaccine, Professor Anne Gershon of Columbia University in New York, who informed me that so far out of over 40 million doses of vaccine distributed,

there are only four instances of transmission and all contact cases were mild. Therefore, there is no need to give varicella zoster immunoglobulin to any contact of a definitely vaccine-associated rash, whether pregnant, immunocompromised or otherwise. If a clinical illness consistent with varicella subsequently occurred in a pregnant or immunocompromised contact, it would be sensible to treat early with aciclovir.

How to decide if the rash is vaccine-associated? Most vaccine-associated rashes occur several weeks after immunisation (median about three weeks), consist of just a couple of papules or vesicles, and are not associated with systemic symptoms. If there are more than just a few lesions, or there are systemic symptoms, and especially if the rash occurs in the first week or two following immunisation, then it is more likely to be due to infection with a wild virus. If you are really uncertain, then err on the side of assuming a wild infection, and give zoster immunoglobulin to high-risk contacts, provided the exposure fits within the guidelines recommended in the Immunisation Handbook.<sup>1</sup>

## Reference

1. National Health and Medical Research Council. The Australian Immunisation Handbook. 8th ed. Canberra: Department of Health and Ageing; 2003. <http://www.immunise.health.gov.au/handbook.htm> [cited 2005 May 10]

## Isomers – correction

Editor, – I need to inform readers of a correction to the article 'Inside the isomers: the tale of chiral switches' (Aust Prescr 2004;27:47-9). On page 47 under Introduction, I cited salmeterol as a single enantiomer drug, however, it is currently marketed as the racemate – noting that the R enantiomer is the active species.

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## Book review

### **Therapeutic Guidelines: Endocrinology. Version 3. Melbourne: Therapeutic Guidelines Limited; 2004.**

**312 pages. Price \$39, students \$25.30, plus postage**

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This familiar yellow book with the metamorphosing tadpole on the cover has further matured and also experienced an expansion in girth (80 pages in three years). It has been extensively revised.

The book aims to provide 'what a clinician needs to know to manage a patient with a given condition'. For commonly encountered clinical conditions in general practice such as diabetes, obesity, thyroid disorders, osteoporosis, contraception, ovarian replacement therapy and menstrual disorders, the guidelines provide excellent summaries of current management recommendations, including drug therapies. It answers

questions that arise in clinical practice. How do you choose between sulfonylureas for a person with diabetes? How do you manage hypoglycaemia in a person on acarbose? How do you monitor and adjust the dose of carbimazole for a person with thyrotoxicosis? How do you interpret bone mineral density results? When should you screen for thrombophilia in a woman who wants the combined oral contraceptive pill? What are the important drug interactions with the combined oral contraceptive pill? How do you overcome the skin irritation when testosterone impregnated adhesive skin patches are used? What happens if a woman with diabetes gets pregnant while on an ACE inhibitor?

These guidelines are well written and easy to read and there are lots of practical points. They are minimally but appropriately referenced with canonical papers. Although the style is definitive, it is not didactic. Where clinical practice is not based on evidence, this is indicated. There are a few minor errors, but these do not detract from the book overall. It represents good value for the money and will be useful for busy practising clinicians, and also medical students. Although time is a valuable resource, I would encourage general practitioners to read through the chapters on conditions they manage frequently.